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CONTENTS

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HEART FAILURE OF THE HUNCHBACK[1]

By T. HANLEY, M. M. PLATTS, M. CLIFTON, AND T. L. MORRIS

(From the University Department of Medicine and the Regional Cardiovascular Centre, Sheffield)

ALTHOUGH the adverse effects of hunchback had been recognized since the time of Hippocrates, it was apparently not realized until the early nineteenth century that the heart may fail in severe kyphoscoliosis. From 1800 onwards much was written on the subject by French and German physicians, and sufficient was known about it for Constantin Paul to include a separate chapter on *Le Cœur des bossus* in his textbook of 1883. Kyphoscoliotic heart disease, as it is now generally termed, was evidently well recognized in England at that time, for Latham, in his lectures to the students of St. Bartholomew's Hospital in 1847, gave a good general account of the heart in spinal deformity. Thereafter surprisingly little attention was paid to this condition in England, and the next report came from Coombs (1930–1), who described four fatal instances of kyphoscoliotic heart disease. More recently there have been many descriptions of the clinical features and morbid anatomy of the heart and lungs in severe hunchback, but relatively few have studied the physiological effects of spinal curvature. The most complete account is still that given in 1939 by Chapman, Dill, and Graybiel, who considered that 'pulmonocardiac failure', a term which they coined to describe the condition of their patients, is 'not analogous to the usual cor pulmonale or to Ayerza's disease'. The present paper deals with the clinical aspects, the arterial blood gases, and the pulmonary function of 24 persons with severe hunchback, with special reference to the differences between those patients who developed congestive heart failure and those who did not.

Patients Investigated and Methods

The patients studied were restricted to those with very severe spinal deformity. As there is no satisfactory method of grading the severity of spinal curvature, we have made facsimiles of the skiagrams of the spine by tracing the outlines of those vertebral bodies which could be identified with certainty. Tracings obtained in this way are shown in Fig. 1, in which each dot indicates a vertebral body.

Tests of pulmonary function. In the majority of the patients measurements were made of the total lung capacity, the residual volume, the vital capacity, the tidal volume, and the inspiratory and expiratory reserve volumes (the

[1] Received April 13, 1957.

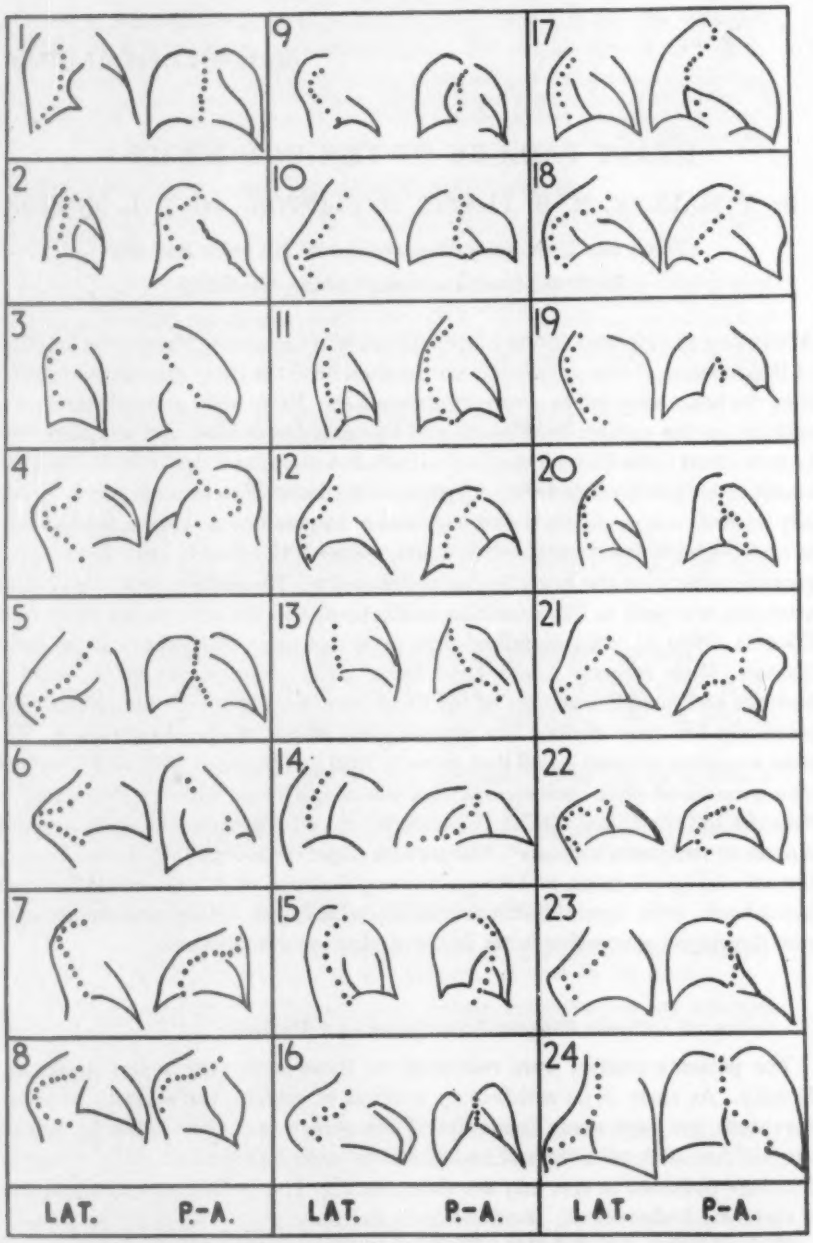

FIG. 1. The shape of the spine in the 24 patients. Nos. 1 to 10 are those with heart failure. The diagram was prepared by reduction of tracings of the postero-anterior and lateral skiagrams. The right-hand figure is the postero-anterior view, and the left-hand the lateral view.

nomenclature employed is that recommended by the Atlantic City Meeting of Physiologists (1950)). These observations were not feasible in all persons (details are given in Table V). The functional residual capacity was determined by the 'helium mixing test', which was carried out by means of the apparatus described by Briscoe (1952). The patient breathed pure oxygen for 15 minutes and then, at the end of a normal expiration, was introduced into a closed gas circuit containing a mixture of oxygen and helium. Carbon dioxide was absorbed by a soda-lime canister. Dilution of the helium occurred with each successive breath, and the rate of fall of the percentage of helium was measured by a katharometer. The volume of the functional residual capacity was calculated from the final reduction in concentration of helium, appropriate corrections being made for changes in temperature and volume of the circuit. The patient's expiratory reserve volume was deducted from the functional residual capacity to obtain the residual volume. An assessment of the severity of pulmonary emphysema, which was arbitrarily graded as 'slight', 'moderate', or 'severe', was made by the graphical method invented and validated by Briscoe (1952). The forced expiratory volume (the volume of air expelled in the first 0·75 second of a forced expiration) was measured by a modified form of the spirometer described by Gaensler (1951). The maximum voluntary ventilation was calculated by multiplying by 40 the forced expiratory volume (Kennedy, 1953; Schilling, Hughes, Dingwall-Fordyce, and Gilson, 1955). Predicted values for the vital capacity and the maximum breathing capacity of adults were derived from the formulae of Baldwin, Cournand, and Richards (1948). These formulae can be expected to give only approximations in deformed patients. Values for children under 15 years were predicted from the formulae of Needham, Rogan, and McDonald (1954).

Arterial blood gases. Blood was taken from the brachial artery in all the patients with heart failure, and in 12 of the 14 patients without heart failure. Blood from the remaining persons was taken without stasis from a superficial vein of the arm, the blood in which had been 'arterialized' by immersion of the limb in water at 118° to 120° F for 10 minutes (Goldschmidt and Light, 1925). The blood pH was measured within a few minutes of collection by using a Cambridge sealed glass-electrode, a Marconi pH-meter, type T511D, and a Stadie anaerobic electrode vessel, the water-jacket of which was at room temperature. The pH was corrected to 38° C by subtracting 0·014 × (38 minus temperature of water in bath) units from the observed value. The total concentration of CO_2, and the oxygen content and capacity of the blood, were measured by the manometric method of Van Slyke and Neill (1924). The plasma bicarbonate concentration and the partial pressure of CO_2 (pCO_2) were derived from the nomogram of Singer and Hastings (1948).

Cardiac catheterization. The nature and purpose of cardiac catheterization were fully explained to the patients, and their consent was freely given. Catheterization of the chambers of the right side of the heart, and of the pulmonary arteries, was carried out by means of a Cournand size 8 catheter. The only form of sedation administered was 500 mg. of methylpentynol ('oblivon')

half an hour beforehand. The catheter was advanced into the pulmonary artery, where the mean blood-pressure was recorded on a saline manometer; the catheter was then attached to a condenser-type manometer, and tracings were obtained of the blood-pressure in the pulmonary artery, the right ventricle, and the right atrium. The zero pressure-level was taken as the surface on which the patient lay, and the tracings were calibrated accordingly. Mean pressures were obtained from the tracings by planimetry.

TABLE I

Clinical Features of Patients with Kyphoscoliosis

Case number	*Sex*	*Age (years)*	*Height (cm.)*	*Weight (kg.)*	*Spinal deformity*		*Pulmonary disease*
					Cause	*Age at onset*	
10 patients with a history of heart failure:							
1	F	63	119	54	Pott's disease	Childhood	Bronchitis
2	M	60	117	48	Rickets	Infancy	Bronchitis
3	F	43	128	34	Collapsed L. lung	5 years	Left empyema. Collapse of left lung at 5 years
4	M	55	142	42	Pott's disease	Childhood	Nil
5	M	54	124	41	Pott's disease	5 years	Bronchitis
6	F	52	115	43	Pott's disease	Childhood	Bronchitis
7	F	45	121	35	Pott's disease	3 years	Bronchitis
8	F	35	138	33	? Poliomyelitis	10 years	Bronchitis
9	M	56	141	38	? Pott's disease	3 years	Bronchitis
10	M	56	151	40	Spondylitis	Childhood	Nil
14 patients who had never had heart failure:							
11	M	18	159	37	Poliomyelitis	13 years	Nil
12	F	15	148	..	Poliomyelitis	7 years	Nil
13	F	47	130	28	Poliomyelitis	Early childhood	Nil
14	M	49	145	67	Rickets	Infancy	Nil
15	F	15	144	..	Poliomyelitis	Childhood	Nil
16	M	34	141	40	Unknown	3 years	Bronchitis
17	M	62	158	60	Unknown	18 years	Nil
18	M	29	173	..	Unknown	?	Nil
19	M	59	140	..	Spondylitis	33 years	Nil
20	F	12	130	30	Congenital hemivertebrae	Infancy	Bronchitis
21	M	55	151	40	Unknown	?	Nil
22	F	24	131	33	Pott's disease	3 years	Bronchitis
23	M	45	146	49	Pott's disease	Infancy	Slight bronchitis
24	M	55	153	49	? Pott's disease	Childhood	Bronchitis

Results

Twenty-four patients were studied, 10 of whom had suffered from congestive heart failure. Five of these 10 patients were seen only after they had recovered from venous congestion and oedema, which was thought in nine instances (Cases 1 to 9) to have been due to true kyphoscoliotic heart disease. In the 10th patient heart failure was not due to kyphoscoliosis, but followed myocardial infarction. Although severe hunchback was present in the remaining 14 patients (Cases 11 to 24), none of these had suffered from heart failure.

Clinical features of kyphoscoliotic heart disease

The occurrence of some important clinical signs is shown in Tables I and II. There were four men and five women, their ages ranging from 35 to 63 years. The spinal deformity consisted of an acutely angular kyphosis without much

scoliosis in four patients, and both kyphosis and scoliosis in five patients (Fig. 1). The convexity of the scoliosis was directed to the right side in all but two patients. In each instance the deformity had arisen in childhood. It seemed likely that changes in the lungs had resulted from the hunchback in all except Case 3, in which this sequence of events was reversed; here a left-sided pneumonia and chronic empyema had led to total collapse of the lung, and the resulting thoracic deformity had caused the kyphoscoliosis. It was difficult to be sure of the cause of the hunchback of each patient. Healed vertebral tuberculosis was the commonest cause.

TABLE II

Cardiovascular Signs in Kyphoscoliotic Patients with Heart Failure

Case number	*Gallop rhythm*	*Pulmonary second sound*	*Cardiac murmurs*	*Tricuspid incompetence*	*Electrocardiogram*
1	Present	Normal	None	Present. Persistent after congestive heart failure	? Slight left ventricular preponderance
2	Present	Normal	None	Present only during congestive heart failure	Right ventricular 'strain' (variable)
3	Present	Normal	None	Present. Persistent after congestive failure	? Slight left ventricular preponderance
4	Absent	Normal	None	Absent	Right ventricular 'strain'
5	Present	Normal	None	Present	Right bundle-branch block
6	Present	Very loud. Widely 'split'	None	Present. Gross. Persistent after congestive failure	Right ventricular 'strain' (variable)
7	Absent	Within normal limits	None	Absent	Right ventricular 'strain'
8	Absent	Very loud. Single	None	Absent	Normal
9	Present	Very loud. Widely 'split'	Systolic	Present only during congestive heart failure	Gross right ventricular hypertrophy
10	Present	Within normal limits	None	Absent	Myocardial infarction

Cardiovascular signs. The signs in the cardiovascular system of eight of the nine patients with heart failure due to kyphoscoliotic heart disease were very similar to those seen in emphysematous patients with anoxic cor pulmonale. The natural history of the disease is illustrated by the progress of these eight persons. Three of the patients who died (Cases 2, 3, and 6) had been observed at intervals from the first appearance of heart failure. The first episode of oedema and venous congestion in Case 2 was followed during the next 16 months by three further attacks. Although the patient recovered well and was able to work after two of these attacks, the third was complicated by a fatal duodenal haemorrhage. The course of the disease was shortest in Case 3; this patient became steadily worse once oedema had appeared, and died in heart failure only four months later. In Case 6, on the other hand, survival occurred after at least five attacks of heart failure over a period of 39 months. Recovery from a single attack of congestive heart failure occurred in four patients (Cases 1, 5, 7, and 8), and only one of these (Case 5) now requires treatment with diuretics. Two others (Cases 1 and 8) remain disabled by dyspnoea, although they are not suffering from heart failure, while the remaining patient (Case 7), who a year ago was in congestive cardiac failure, has made an excellent recovery, and has

since remained at work. All but one of these persons had been subject to recurrent attacks of bronchitis, and an acute exacerbation of their respiratory infection was almost invariably responsible for precipitating heart failure.

Clinical examination of the heart itself rarely revealed gross physical signs (Table II). The apex beat was often difficult to feel, and none of the patients showed great cardiac enlargement. Considerable displacement of the heart was found only in Case 8, in which the cardiac impulse could easily be felt in the fourth right intercostal space. A systolic pulsation in the left lower parasternal area suggested some right ventricular enlargement in five patients. Cardiac murmurs were absent except in Case 9; in this patient a faint systolic bruit was audible in the pulmonary area. On the other hand, a gallop rhythm was often present, and in some patients persisted when congestive cardiac failure had gone. The second sound at the base of the heart was very loud in three patients, and widely 'split' in two of these. It is difficult to know how reliably these changes indicate elevation of the pulmonary artery blood-pressure when they are found in association with severe hunchback, as the topography of the heart may be so abnormal as to make it impossible to distinguish the aortic and pulmonary second sounds. For example, in Case 8, with displacement of the heart into the right side of the thorax, an extremely loud but single second sound was heard at the base of the heart; cardiac catheterization, however, showed only a slight rise of blood-pressure in the pulmonary artery (Table VI). Systolic pulsation of the jugular veins and the liver, indicating incompetence of the tricuspid valve, was seen in six patients. When the patients became free from oedema the signs of tricuspid incompetence usually vanished, but in Case 3 they persisted until death four months later. Tricuspid incompetence continued for at least a year before death in Case 6. The jugular veins also showed very prominent presystolic '*a*' waves in two patients. More striking than the signs found on examination of the heart were the peripheral circulatory signs. Undue warmth and flushing of the extremities and a full, abrupt pulse, together with severe central cyanosis, dominated the clinical picture. No disturbances of cardiac rhythm were encountered; even extrasystoles were uncommon, and tachycardia was not a prominent feature. There were no signs suggesting obstruction of the aorta in any patient. The blood-pressure in the arms was a little raised in two, and was normal in the others; it was not recorded in the lower limbs, but free pulsation of the femoral arteries could be felt in all cases.

Respiratory system. There were no characteristic signs. The breathing was restricted and laboured and, where scoliosis was severe, little movement was observed on the side facing the concavity of the scoliosis. Crepitations at the lung bases were common, but there were no signs of collapse or other local disease of the lungs, except in Case 3 (Table I). It was remarkable that, although the majority of these patients had suffered repeated attacks of bronchitis, signs of bronchospasm were very slight or absent.

The arterial blood gases and pulmonary function tests in kyphoscoliotic heart disease

Arterial blood gases. Details of all observations are given in Table III.

Analysis of the arterial blood gases both in failure and after recovery was possible in two patients. Eight patients were anoxic, and in these persons the arterial pCO_2 was raised and the plasma showed the other biochemical features of 'compensated' chronic respiratory acidosis, that is, increased acidity of the blood and a high concentration of bicarbonate in the plasma. The severity of CO_2-retention was roughly proportional to the degree of anoxia, and was greater

TABLE III

Arterial pH, pCO_2, Oxygen Saturation, and Haematocrit Level in 24 Patients with Kyphoscoliosis

Case number	*pH*	*Plasma bicarbonate (m-equiv./l.)*		*pCO_2 (mm. Hg)*	*Oxygen capacity (vols. %)*	*Oxygen saturation (%)*	*Packed cell volume (%)*
Patients with history of heart failure:							
1	7·34	38·3	In failure	75	20·8	66	46
	7·31	32·3	Recovered	64	19·2	73	46
2	7·33	38·1	In failure	74	20·8	68	52
	7·33	28·1	Recovered	55	20·8	83	..
3	7·39	38·0	In failure	65	21·1	71	48
4	7·32	30·3	Recovered	60	20·0	85	49
5	7·38	31·7	„	55	20·4	71	39
6	7·34	27·4	„	52	18·2	71	52
7	7·32	30·2	„	60	18·9	79	46
8	7·38	29·3	„	51	21·4	78	39
9	7·36	21·8	„	41	18·6	89	47
10	7·41	19·6	„	33	20·4	93	50
Patients with no history of heart failure:							
11	7·34	32·7	..	61	18·5	78	58
12*	..	26·0	..	..	..	..	..
13	7·43	25·2	..	39	17·5	94	38
14	7·49	26·9	..	36	20·6	97	47
15	7·42	26·2	..	42	18·7	91	41
16	7·36	25·3	..	48	20·3	93	50
17	7·38	31·8	..	54	16·1	94	42
18	7·39	26·9	..	45	19·2	81	43
19	7·43	28·9	..	47	10·5	92	28
20*	7·38	23·2	..	41	18·4	..	40
21	7·43	26·3	..	41	16·7	90	47
22	7·37	20·3	..	37	21·5	94	38
23	7·40	30·1	..	49	18·0	93	44
24	7·42	23·7	..	37	17·5	100	43

* 'Arterialized' sample.

when heart failure was present than after recovery, though even at their best these patients had a high arterial pCO_2. Thus in Cases 1 and 2 the pCO_2 was 75 and 74 mm. Hg during heart failure, and diminished to 64 and 55 mm. Hg when recovery had occurred, while the oxygen saturation rose simultaneously by 7 per cent. and 15 per cent. In Case 2 death occurred in another bout of heart failure, and on this occasion there was more severe anoxia, the oxygen saturation falling to 41 per cent. Patient No. 3, in the early stages of her single intractable attack of heart failure, had an oxygen saturation of 65 per cent,, which ultimately fell to 32 per cent. In Cases 2 and 3 inhalation of oxygen in this final phase of extreme anoxia raised the arterial oxygen saturation almost to

normal. Respiration was, however, so depressed by the relief of anoxia that, on resumption of breathing atmospheric air, cyanosis became intense, the arterial pCO_2 rose abruptly, and the blood pH fell to very low levels (Table IV). In four instances the blood gases were analysed only when recovery from heart failure had occurred. In three of these patients a moderate degree of anoxia persisted, the oxygen saturation being 71, 79, and 78 per cent. in Cases 6, 7, and

TABLE IV

The Effect of Inhalation of Oxygen in the Terminal Stages of Anoxic Kyphoscoliotic Heart Disease (Case 2)

	Arterial blood		
	Oxygen saturation (%)	*pH*	*pCO_2 (mm. Hg)*
Before inhalation of oxygen	41	7·19	74
In 7th minute of oxygen inhalation	85	7·14	83
In 9th minute after resumption of breathing room air .	31	7·05	105

8, and in each instance there was detectable cyanosis. In Case 4 the patient, when not in heart failure, was only slightly anoxic (saturation 85 per cent.). The arterial pCO_2 of these four patients ranged from 51 to 60 mm. Hg.

The arterial oxygen capacity and haematocrit level in all the patients lay within the normal range (Table III).

Pulmonary function tests. The results in eight of the patients with a history of heart failure are shown in Table V. Except in Case 3 the pulmonary function tests were carried out after recovery from heart failure. These results may conveniently be compared here with the findings in the 14 patients who had not had heart failure. In those with and those without heart failure the characteristic change was a great reduction of the total lung capacity, the vital capacity, and the maximum voluntary ventilation. The helium mixing test, however, showed surprisingly little evidence of impaired mixing of gas in the lungs. A large proportion of the vital capacity was employed as tidal volume at rest. In normal persons this proportion ranges from 10 to 20 per cent.; the average in the kyphoscoliotic patients without heart failure was 33 per cent., and in those with a history of heart failure 42 per cent. (Fig. 2). It was not possible to separate sharply the patients who had had heart failure from those who had not by any single test of pulmonary function. Fig. 3 compares the pulmonary function of seven patients suffering from kyphoscoliotic heart disease with that of seven patients of similar age and sex with heart failure due to emphysema. The kyphoscoliotic group had no difficulty in performing rapid expiration; six were able to expel more than 63 per cent., and one 55 per cent., of their vital capacity in 0·75 second. By contrast, the emphysematous patients expelled only 18 to 44 per cent. The forced expiratory volume gives an indication of the resistance to air-flow through the lungs: the low values in the emphysema group are largely due to bronchospasm, from which the kyphoscoliotic patients were singularly free. All the emphysematous patients had severe impairment of intrapulmonary mixing of gas, but the kyphoscoliotic persons had normal or

TABLE V

The Pulmonary Function of 22 Kyphoscoliotic Patients

(a) Case number	(b) Surface area (sq. m.)	(c) Predicted vital capacity (l.)	(d) Vital capacity (Geneter) (l.)	(e) Vital capacity as % of predicted	(f) Volume of vital capacity expired in first 0·75 sec. (l.)	(g) % of vital capacity expired in first 0·75 sec.	(h) Tabbest maximum voluntary ventilation (l./min.)	(i) Inspiratory reserve volume (l.)	(j) Expiratory reserve volume (l.)	(k) Tidal volume (l.)	(l) Vital capacity (l.) (sum of 'f', 'j', and 'k')	(m) Tidal volume as % of vital capacity	(n) Respiratory rate	(o) Minute-volume of alveolar ventilation ((tidal volume − 150 ml.) × respiratory rate)	(p) Residual volume (l.)	(q) Total lung capacity (l.)	(r) Residual volume as % of total lung capacity	(s) 'Uneven mixing' grade
Eight patients who had suffered from heart failure:																		
1	1·42	2·19	0·36	16	0·34	94	13·5	0·18	0·09	0·29	0·56	52	19	2·66	1·12	1·62	69	0*
2	1·20	2·90	1·07	37	0·76	70	30·4	0·59	0·34	0·39	1·12	35	14	3·36	1·20	2·32	52	1
3	1·01	2·28	0·67	29	0·55	80	22·0	0·17	0·24	0·25	0·66	38	24	2·40	0·42	1·08	39	1
4	1·28	3·06	0·99	32	0·61	64	24·4	0·38	0·24	0·38	1·00	38	26	5·97	1·07	2·07	52	1
5	1·14	2·66	0·61	23	0·44	73	17·8	0·20	0·08	0·37	0·65	52	14	3·08	0·72	1·37	53	1
8	1·05	2·52	0·65	26	0·36	55	14·4	0·24	0·19	0·29	0·72	40	22	3·08	0·53	1·25	42	1
9	1·23	3·08	0·76	25	0·55	86	22·0	0·36	0·17	0·37	0·90	41	18	3·96	0·13	1·03	13	1
10	..	2·96	1·61	54	1·30	80	52·0	0·75	0·37	0·41	1·53	27	24	6·24	1·22	2·75	44	0
14 patients without a history of heart failure:																		
11	1·31	4·08	0·77	19	0·66	86	26·4	0·26	0·13	0·26	0·65	40	22	2·42	0·55	1·20	46	1
12	1·64	3·00	1·13	38	0·92	86	36·7	0·50	0·22	0·26	0·98	27	28	3·08	0·56	1·54	36	0
13	1·01	2·22	0·77	35	0·65	86	26·0	0·18	0·28	0·34	0·80	43	21	3·98	0·80	1·60	50	0
14	..	3·20	2·08	65	1·60	77	64·0	1·03	0·50	0·55	2·08	27	16	6·40	1·44	3·52	41	1
15	1·68	1·95	0·87	59	0·87	100	35·0	0·26	0·23	0·23	0·72	32	24	1·92	1·52	2·24	68	1
16	1·25	3·36	0·85	25	0·75	87	30·1	0·26	0·26	0·48	1·00	48	18	5·04	1·00	2·00	50	1
17	1·61	3·27	1·64	50	1·11	68	44·0	0·49	0·58	0·39	1·46	27	16	3·84	1·35	2·81	48	1
18	..	4·20	1·99	47	0·99	78	39·7	0·61	0·74	0·72	2·07	35	29	16·53	1·37	3·44	40	1
19	..	2·95	1·74	59	1·31	75	52·4	0·93	0·42	0·38	1·73	22	18	4·14	2·28	4·01	57	0
20	0·74	1·14	0·67	76	0·77	88	30·8	0·35	0·31	0·32	0·98	33	24	4·08	..	..	..	..
21	1·30	3·22	1·34	42	0·92	68	36·5	0·49	0·36	0·49	1·34	37	19	6·46	1·73	3·07	56	0
22	1·08	2·54	1·08	43	0·81	75	32·4	0·49	0·19	0·38	1·06	36	24	5·52	0·71	1·77	40	1
23	1·39	3·30	1·37	42	0·58	42	23·2	0·27	0·24	0·61	1·12	54	14	6·44	3·12	4·24	74	2
24	1·49	3·45	2·85	83	1·05	37	42·0	0·92	1·09	0·41	2·42	17	19	4·94	3·21	5·63	57	1

* 0 = normal. 1 = slight impairment. 2 = moderate impairment.

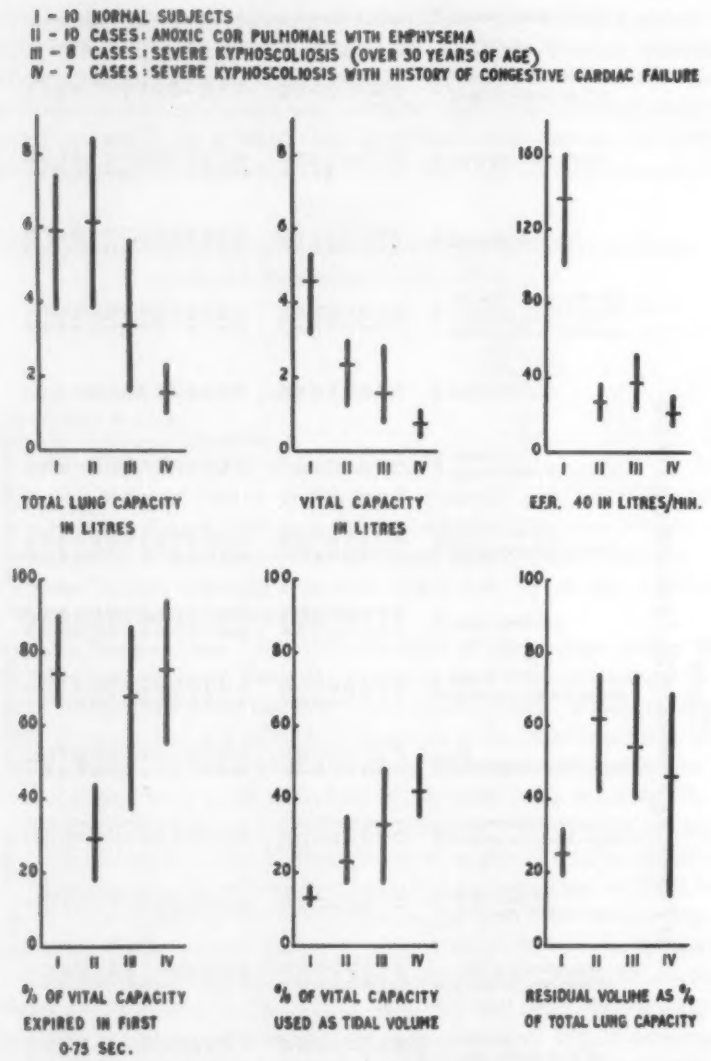

FIG. 2. Diagram to illustrate the degree to which various tests of pulmonary function differentiate between kyphoscoliotic patients with and without heart failure. The findings in 10 normal persons and 10 patients with emphysema are included for comparison. Kyphoscoliotic patients less than 30 years of age have been excluded, in order to make the ages of the groups roughly comparable.

The vertical lines represent the range, and the horizontal intersections the mean, of the observed values. E.F.R. 40 = indirect maximum voluntary ventilation.

only slightly uneven mixing. It may be seen from Fig. 3 that the fraction of the total lung capacity occupied by the residual volume was greater than normal in all but one of the kyphoscoliotic subjects, and only in this respect did they resemble the patients with emphysema.

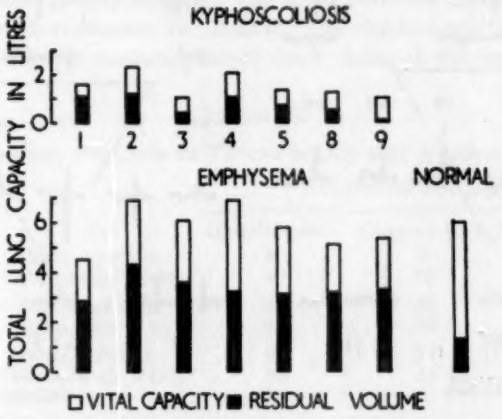

FIG. 3. The difference between the volumes of the 'compartments' in emphysema and kyphoscoliotic heart disease. The kyphoscoliotic patients have a very small total lung capacity, and their residual air has a small absolute volume, but is a higher proportion than normal of the total lung capacity.

Electrocardiogram. Four patients showed the pattern of right ventricular 'strain', with inversion of T waves in the right-sided praecordial leads (Fig. 4 *a*). One had complete right bundle-branch block. Two patients showed a very deep S wave in leads V2 and V3, and some left axis deviation, findings which suggest left ventricular hypertrophy (Fig. 4 *c*). Neither of these patients showed any clinical or radiographic indication of left ventricular hypertrophy, however, and at autopsy in Case 3 the right ventricle weighed more than the left. Case 9 differed from the other instances of heart failure in showing a normal arterial pCO_2 (41 mm. Hg) and only slight anoxia, the arterial oxygen saturation being 89 per cent. The patient had a very loud double pulmonary second sound, with palpable closure of the pulmonary valves. As he had no lateral displacement of the heart, it seems probable that these signs indicated pulmonary hypertension, but confirmation of this by catheterization was not possible. He was the only patient with electrocardiographic signs of great right ventricular hypertrophy (Fig. 4 *d*).

Kyphoscoliosis without heart failure

No special attempt was made to match the ages of the patients in the groups with and without heart failure, and the only criterion for selection of Cases 11 to 24 was the presence of very severe spinal deformity (Fig. 1). The patients' ages ranged from 12 to 62 years, six being more than 45 years old (Table I). They resembled the heart-failure group in that the spinal deformity had been

acquired in childhood in almost every instance, but differed in that they seldom had a history of recurrent pulmonary infections. The severity of their disability varied widely, but was greatest in those whose hunchback was due to poliomyelitis, and who had in addition paralysis of the diaphragm or the intercostal

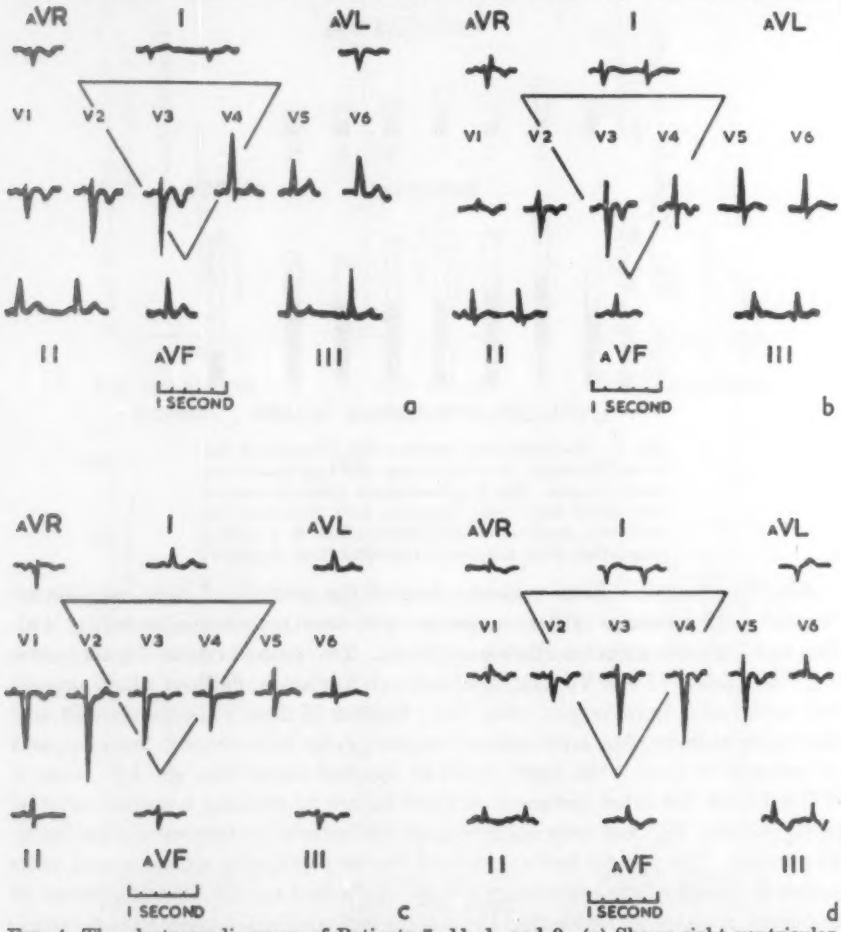

FIG. 4. The electrocardiograms of Patients 7, 11, 1, and 9. (*a*) Shows right ventricular 'strain' in Case 7. (*b*) Shows right ventricular hypertrophy and 'strain' in a boy of 18 (Case 11), whose kyphoscoliosis was due to poliomyelitis. He had not had heart failure, but showed anoxia and a retention of carbon dioxide. (*c*) Shows apparent left ventricular preponderance in Case 1. (*d*) Shows the pattern of advanced right ventricular hypertrophy and 'strain' in Case 9. This was the only patient with true kyphoscoliotic heart disease who was not anoxic and hypercapnic.

muscles. Except for Case 11, on which a separate comment is made below, none of them showed any abnormal cardiovascular signs, and none was cyanotic. The electrocardiogram showed several instances of rather unusual degrees of rotation of the heart axis, but only in Case 11 was there inversion of the T waves in the right-sided praecordial leads (Fig. 4 *b*).

The arterial oxygen saturation was 90 per cent. or more in all but two patients, and in only two instances did the arterial pCO_2 exceed 50 mm. Hg (Table III). In Cases 11 to 22 there were changes in pulmonary function which were similar in kind to those of the patients with heart failure, in that the vital and total lung capacities were greatly reduced. The lungs were well ventilated, and there was no increase of resistance to air-flow. The pulmonary function tests in Cases 23 and 24 gave results different from those of the remainder. Both

TABLE VI

Intracardiac Pressures in Three Patients with Kyphoscoliosis

Case number	*Site*	*Pressure in mm. Hg*		
		Systolic (peak)	*Diastolic (end)*	*Mean*
4	Right ventricle	40	10	19
	Pulmonary artery	40	23	29
8	Right ventricle	50	18	28
	Pulmonary artery	48	30	36
23	Right ventricle	40	26	24
	Pulmonary artery	45	25	31

patients had a relatively large total lung capacity (4·24 and 5·63 litres), with a much increased residual volume (3·12 and 3·21 litres). Their forced expiratory volume was greatly reduced, and the helium mixing tests showed moderate impairment of intrapulmonary gas mixing in one patient and slight impairment in the other. Case 11 was of especial interest. The patient was the only person in the group without heart failure who had anoxia, hypercapnia, and electrocardiographic evidence of right ventricular hypertrophy.

Findings on cardiac catheterization

Cardiac catheterization was carried out in three patients (Cases 4, 8, and 23), two of whom (Cases 4 and 8) had previously had oedema and venous congestion, but were not in heart failure when catheterized, although still moderately anoxic. The systolic and diastolic blood-pressures in the right ventricle and pulmonary artery were slightly raised in Cases 4 and 23, and moderately raised in Case 8 (Table VI).

Discussion

The present work compares the pulmonary function and arterial blood gases of a group of patients with severe spinal deformity who had suffered from heart failure with those of an equally deformed group who had not. The aim was to seek for differences which might help to elucidate the cause of 'heart failure of the hunchback'. The results show that in severe kyphoscoliosis the vital capacity and the total capacity of the lungs may be greatly reduced, but that the diminished volume of lung tissue is evenly ventilated. The evenness of gas distribution in the lungs of these persons, and their ability to exhale a large fraction of the vital capacity in three-quarters of a second, reflect the lack of

bronchial obstruction found in kyphoscoliosis as compared with chronic bronchitis and emphysema. In severe spinal deformity the residual air is often an abnormally large part of the total lung capacity, but this is probably due to mechanical restriction of expiration rather than any 'poorly ventilated space' in the lungs, such as is found in emphysema. In spite of the efficiency of pulmonary ventilation, the total amount of lung available for respiratory gas exchange may be so reduced by severe hunchback that the reserve of function is negligible, and it is well known that acute pulmonary infections, or depression of ventilation by quite small doses of hypnotics or morphine, may rapidly prove fatal. It has been emphasized in the results that heart failure is also precipitated by acute exacerbations of bronchitis, and in the management of patients who have once developed heart failure the prophylaxis and treatment of such infections is of first importance.

While there seems to be good reason for believing that heart failure in kyphoscoliosis is a consequence of impaired lung function, the mechanism in this disease is no less obscure than in emphysema. In the deformed patients studied the impairment of pulmonary function was, broadly speaking, more severe in those who had suffered from heart failure than in those who had not, but, as shown in Fig. 2, the two groups could not be sharply distinguished merely by measurements of the various lung volumes. On the other hand, the arterial blood-gas values separated the groups distinctly, with the exception of Cases 9 and 11. The only previous detailed study of the pulmonary function and arterial blood gases in kyphoscoliosis was reported in 1939 by Chapman, Dill, and Graybiel, whose results are summarized in Table VII. The present results are entirely in agreement with their findings as regards the effects of hunchback on pulmonary function, but the blood-gas values in the two series are quite different. In all but one of Chapman, Dill, and Graybiel's patients the arterial oxygen saturation exceeded 93 per cent. and the pCO_2 was less than 49 mm. Hg; this is in contrast with the anoxia and hypercapnia of our patients with heart failure (Table III). The disagreement in results is due to differences in the type of patients studied. Only one of Chapman, Dill, and Graybiel's patients with 'pulmonocardiac failure' had congestive heart failure, and in this person neither pulmonary function nor the blood gases were studied. The present work, on the other hand, has been concerned specifically with the differences between those who had and those who had not suffered from oedema and venous congestion.

In emphysema, as well as in kyphoscoliosis, the occurrence of congestive heart failure is closely associated with arterial oxygen unsaturation and hypercapnia (Platts, 1953). It is, however, not known whether these changes in the blood gases are causal factors in the development of heart failure or merely associated phenomena. Bates, Knott, and Christie (1956) in their long-term study of emphysema found that 'the onset of evident right ventricular failure is heralded by a falling diffusing capacity'. In the light of their findings it would be of interest to compare the oxygen diffusing capacity of the lungs in the present two groups of patients with hunchback. Yet the changes in the arterial

blood gases of our patients with hunchback also appear to distinguish those who develop heart failure from those who do not, and these changes cannot be ascribed to impaired diffusion. Carbon dioxide is roughly 20 times more diffusible than oxygen through the alveolar membrane, and a fall of diffusing capacity consequently causes profound reduction of the oxygen tension of the blood before an appreciable rise of carbon-dioxide tension develops. The combination of a high arterial pCO_2 with a moderate reduction of oxygen saturation indicates that alveolar ventilation is insufficient.

TABLE VII

Arterial Blood Gases in Kyphoscoliosis

Data of Chapman, Dill, and Graybiel (1939) for comparison with Tables III and V

Subject	I.P.	A.P.	L.S.	R.B.	W.C.	W.D.	M.N.
Cause of deformity	Polio-myelitis	Polio-myelitis (?)	Polio-myelitis	?	Polio-myelitis (?)	Polio-myelitis	Polio-myelitis
Vital capacity (ml.)	700	1,460	1,330	2,230	2,520	1,220	..
Residual air (ml.)	1,300	1,720	1,295	1,955	3,530	1,115	..
Total lung volume (ml.)	2,000	3,180	2,625	4,185	6,050	2,335	..
Residual air as % of total lung volume	65	54	49	47	58	48	..
Arterial oxygen saturation (%)	95·3	95·9	93·4	95·4	86·1	97·5	93·7
Arterial pCO_2 (mm. Hg)	44·9	46·0	39·9	43·0	44·5	48·5	41·6

One way in which anoxia and hypercapnia might contribute directly to heart failure is by a vasoconstrictive action on the pulmonary circulation. Since von Euler and Liljestrand reported in 1946 that inhalation of air with a low oxygen tension or high carbon-dioxide tension constricted the lung vessels of anaesthetized cats, a great many attempts have been made, both in animals and in man, to define the role of the blood gases in the regulation of pulmonary vascular tone. The results have, however, been very conflicting, and experimental artifacts difficult to exclude. The recent studies of Nahas, Visscher, Mather, Haddy, and Warner (1953–4) in dogs, and Fishman, Himmelstein, Fritts, and Cournand (1955) in man, suggest that anoxia does not in fact increase resistance to the flow of blood through the lungs. The effects of a high carbon-dioxide tension have been less thoroughly investigated. Bean, Mayo, O'Donnell, and Gray (1951) found that a high carbon-dioxide tension of blood perfusing the isolated lungs of dogs had different effects on the various pulmonary vessels, probably constricting the venules but dilating the arterioles.

The present studies by cardiac catheterization of kyphoscoliotic patients were few, and were deficient in that measurements of pressure were made only in the absence of oedema and venous congestion. In the two persons who were still anoxic when observations were made, the pulmonary arterial pressure was slightly raised, the levels being comparable with those found by Whitaker (1954) in his patients with emphysema who were recovering from heart failure. Few other measurement of the pulmonary arterial pressure of kyphoscoliotic patients have been recorded. Bloomfield, Lauson, Cournand, Breed, and Dickinson (1946) included one patient with hunchback, who also had systemic hypertension, in their study of 70 persons with chronic pulmonary disease, and in this instance the pulmonary systolic pressure was slightly raised (36 mm. Hg).

Lewis, Daines, Samuels, and Hecht (1952) described a girl aged 13 years, with severe kyphoscoliosis due to congenital hemi-vertebrae, who died of heart failure. Three months before death, when she was not in heart failure, the pulmonary arterial blood-pressures were greatly elevated (systolic pressure 138 mm. Hg, diastolic 58 mm. Hg). Pulmonary hypertension of such severity is almost certainly due to structural changes in the pulmonary circulation. The pulmonary vessels of two of our patients who died of kyphoscoliotic heart disease did not show the histological changes commonly associated with severe pulmonary hypertension, and the present results suggest that permanent and severe pulmonary hypertension is not essential for the development of congestive heart failure in the hunchbacked. On the other hand, it is possible that the close relation between acute exacerbation of bronchitis and the development of heart failure is due to sudden transient rises of pulmonary arterial pressure associated with pulmonary infection.

Our thanks are due to Professor C. H. Stuart-Harris and Dr. James W. Brown for their encouragement and for facilities provided in their departments, and to Dr. C. E. Davies for much help in preparation of the manuscript. We are most grateful to those who referred patients to us, including Mr. A. G. Taylor, Dr. C. E. Davies, Dr. E. G. Rhind, Mr. J. T. Chesterman, Mr. E. G. Herzog, Dr. C. S. Darke, Dr. C. W. Lawson, Dr. H. Morrow Brown, and Dr. B. Burns. Valuable technical assistance was given by Miss M. S. Greaves, Miss N. Hardy, Mrs. D. Warrender, and Mr. D. Woolhouse.

Summary

1. The clinical features, arterial blood-gas values, and pulmonary function of 10 patients with severe kyphoscoliosis and heart failure are described. The results in these patients are compared with those obtained in 14 persons who had severe spinal curvature but had not suffered from heart failure.

2. Severe kyphoscoliosis may reduce the total lung capacity and the vital capacity to as little as one-quarter of normal. The diminutive lungs are, however, ventilated with an efficiency only a little less than normal, and 'emphysema' is usually slight.

3. The diagnosis of kyphoscoliotic heart disease did not present great difficulty. In kyphoscoliotic heart failure peripheral vascular signs were predominant, and the clinical picture closely resembled that of anoxic cor pulmonale due to emphysema.

4. Reduced arterial oxygen saturation and retention of carbon dioxide were found in eight of the nine patients with true kyphoscoliotic heart disease, but these changes were present in only two of the 14 patients without heart failure. It was not possible to make such a clear distinction, simply by measuring either the volumes of the various 'compartments' of the lungs or the efficiency of ventilation, between those with and those without a history of heart failure.

5. Cardiac catheterization was done in three patients, and showed a moderate rise of the pulmonary artery blood-pressure in two anoxic patients who had recovered from heart failure, and a small rise in one patient who had not had heart failure.

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HEREDITARY CAPILLARY PURPURA[1]

(*Von Willebrand's Disease*)

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Until the beginning of this century all hereditary haemorrhagic disorders were regarded as haemophilia, irrespective of their clinical or genetic characteristics. Sir William Osler established hereditary haemorrhagic telangiectasia as a separate entity in 1901, after earlier reports by Babington (1865), Legg (1876), and Rendu (1896). Some years later, with the publication in 1913 of a paper by Austin and Pepper, it became apparent that there was a third variety of hereditary haemorrhagic disorder which bore a closer resemblance to the purpuras than to haemophilia. Austin and Pepper reported a haemorrhagic state in two female patients who each had a strong family history of bleeding; the distinction from haemophilia was not made, although the patients affected were female and the coagulation times were normal. There followed the report by Glanzmann (1918) of a haemorrhagic state which he ascribed to a functional abnormality of the blood-platelets, and to which he gave the name of 'hereditary haemorrhagic thrombasthenia'. Later authors described patients in whom an inherited tendency to bleed excessively was accompanied by a prolonged bleeding time, but in whom the platelet count and coagulation time were normal (Rosenfeld, 1921; Buckman, 1928; Giffin, 1928; Little and Ayres, 1928; Minot, 1928; Rothman and Nixon, 1929). Von Willebrand in 1931 published the largest series up to that date, having studied a family of bleeders in the Aaland Islands. Twenty-three members of a family of 66 complained of haemorrhagic symptoms consisting of bleeding on trivial injury, or spontaneous bleeding from the nose, gums, skin, genitals, or gastrointestinal or urinary tracts. The platelet counts were normal, as was the platelet morphology, but the bleeding time was greatly prolonged and the tourniquet test positive; coagulation time and clot retraction were normal. Von Willebrand at first named the condition 'hereditary pseudohaemophilia', a name which has since been applied to other haemorrhagic diseases. He considered that there might be a lesion of the capillary walls but, like Glanzmann, preferred the explanation of a functional platelet defect. As a result of experiments intended to show the inability of the platelets to occlude a glass capillary tube, he renamed the condition 'constitutional thrombopathy' (von Willebrand and Jürgens, 1933).

Examples of the hereditary disease described by von Willebrand have since

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been reported by Farber (1934), Weeks (1934), Bailey and McAlpin (1935), Fowler (1937), Geiger and Evans (1938), Carpenter and Allen (1941), Morhardt (1942), Perkins (1946), Levy (1947), Halliwell and Brigham (1948), Cazal and Izarn (1950), Lelong and Soulier (1950), Goudemand and Samaille (1953), and Macfarlane and Simpkiss (1954). Extensive reviews of the literature have been made by Estren, Médal, and Dameshek (1946), Revol, Favre-Gilly, and Ollagnier (1950), and Buchanan and Leavell (1956). It is our purpose to describe the clinical features of this condition, and to discuss its classification in the light of the tests which are now available for the investigation of haemostasis.

The Classification and Frequency of the Hereditary Purpuras

The arrest of haemorrhage in the normal subject can be regarded as occurring in two stages. The first involves the occlusion of the injured capillary by its own contraction, aided by agglutination of platelets at the site of injury, and the second the coagulation of the blood. This sequence was demonstrated by Macfarlane (1941), who observed microscopically the changes which occurred in the capillaries of the human nail-bed on injury. In studying the capillaries of patients with various haemorrhagic disorders, Macfarlane showed that in those with a prolonged bleeding time the capillaries appeared abnormal and responded inadequately to puncture. The mechanical action of the blood-platelets in aiding capillary occlusion has been demonstrated by M. B. Zucker (1947) and H. D. Zucker (1949). Besides contributing to the first stage of the haemostatic mechanism, however, platelets are also essential for the coagulation of the blood, being a component of the thromboplastin-generation complex (Biggs and Douglas, 1953; Biggs, Douglas, and Macfarlane, 1953).

The defect in von Willebrand's disease occurs in the first stage of the process of haemostasis, that concerned with vascular occlusion. Macfarlane (1941) has shown by microscopical examination that there is irregularity and tortuosity of the nail-bed capillaries, and inadequate contraction on injury. These abnormalities result in a prolonged bleeding time. The name 'hereditary capillary purpura', or von Willebrand's disease, is best reserved for cases of this kind, in which the defect is apparently confined to the walls of the capillaries. In a much rarer variety of hereditary purpura there is evidence of a defect in the platelets, in that clot retraction is poor, prothrombin consumption is reduced, or thromboplastin generation is impaired. This type of hereditary purpura, in which a functional platelet defect is demonstrated in the presence of a normal platelet count, is best referred to as hereditary thrombocytopathic purpura, or Glanzmann's disease. Equally rare is hereditary thrombocytopenic purpura, in which the platelets are reduced in numbers. Finally, there are cases in which a capillary defect is combined with the deficiency or absence of a clotting factor. The main body of this paper will be confined to hereditary capillary purpura, the rarer hereditary purpuras being referred to later.

In our experience hereditary capillary purpura is the second commonest

hereditary haemorrhagic disorder. In a series of 80 cases of hereditary haemorrhagic disorders seen in Oxford, 52 were examples of haemophilia or Christmas disease, 19 of hereditary capillary purpura, seven of hereditary haemorrhagic telangiectasia, one of congenital afibrinogenaemia, and one of a dual haemostatic defect.

Diagnostic Criteria and Selection of Cases

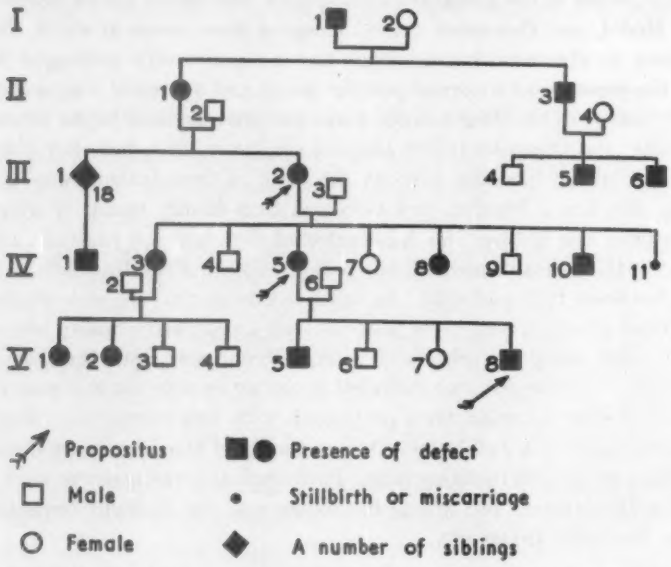
In their review of the literature dealing with 'hereditary pseudohaemophilia', Estren, Médal, and Dameshek (1946) accepted those cases in which there was a tendency to abnormal haemorrhage and a significantly prolonged bleeding time in the presence of a normal platelet count and a normal coagulation time. A family history of bleeding was not a *sine qua non*. In their larger series Revol, Favre-Gilly, and Ollagnier (1950) adopted similar criteria, but they did include one patient whose bleeding time at the time of examination was only four minutes. He was a bleeder, and belonged to a family many of whom were sufferers from the disease. We have selected for study 20 patients who were observed in the wards or medical out-patient clinics of the Radcliffe Infirmary, Oxford, between 1937 and 1954. In order to ensure that we were dealing with the inherited disorder, only those patients with a suggestive family history were included. Also, using the criteria of Estren, Médal, and Dameshek, and Revol, Favre-Gilly, and Ollagnier, we included in the series only those whose bleeding time had on some occasion been prolonged, with two exceptions. Both these patients belonged to a well-known Oxford family of bleeders, other members of which had a prolonged bleeding time. Pathological investigations were carried out in the Department of Clinical Pathology and the Nuffield Department of Medicine, Radcliffe Infirmary.

Age and Sex Incidence

In their review of the literature, Buchanan and Leavell (1956) found that the condition affects both sexes, with a slight preponderance of female subjects (104:95). Von Willebrand himself, in the families he studied, found that 16 out of 35 women were affected, but only seven out of 31 men. Although of our 20 patients 15 were female and five male, the total number of either sex affected among their relatives was approximately the same. The disease is usually recognized early in life. Our patients, when seen in hospital, varied in age from a few months to 62 years, but all manifested some haemorrhagic symptom dating back to their childhood, and in many cases from birth. Patient No. 8 had a tendency to bruise and bleed easily from birth, and bled on separation of the umbilical cord. Similarly, the baby born to another patient (Case 6) bled from the umbilicus at birth, and vomited blood shortly afterwards. Most of the other patients became aware that they bruised and bled easily at a later date, and it sometimes happened that a new symptom became particularly troublesome in later life, such as haematuria in Case 13 and menorrhagia in Case 15.

Heredity

While the disease is generally accepted as a Mendelian dominant, the pattern of inheritance is by no means constant. Because of the preponderance of female patients in his series, von Willebrand considered the inheritance to be that of a sex-linked dominant with the gene carried on the X chromosome. Favre-Gilly, Guy, Beaudoing, and Roger (1954) have gone carefully into the literature



Hereditary capillary purpura (von Willebrand). Family pedigree of Cases 17 (III. 2), 18 (IV. 5), and 19 (V. 8).

of the heredity of this disease, and analysed the reports of 26 families. Sixteen showed a simple dominant pattern of inheritance, three a sex-linked dominant pattern with the gene carried on the X chromosome, and two with the gene carried on the Y. Four were quoted as examples of simple recessive inheritance, and one as a sex-linked recessive. Fourteen of our 20 patients showed an inheritance according to an autosomal dominant pattern. We illustrate one such pedigree. In the remaining six cases the pattern of inheritance was ill-defined. One patient (Case 1) had a maternal uncle who was known to have bled to death, and another (Case 10) had two affected siblings. The father of a third patient (Case 12) suffered from epistaxes all his life, and another (Case 15) had a sister whom she described as a bleeder. In Case 14 the patient had two male relatives on his mother's side known to be bleeders. The sixth patient (Case 11) had no relatives with a bleeding tendency, but her parents were full cousins, and she also had the inherited trait of albinism. Her illness may therefore have been inherited as a simple recessive, or it may have arisen as a mutation.

The Clinical Picture

Haemorrhage in hereditary capillary purpura may be either spontaneous or provoked by trauma, sometimes of a trivial nature. Frequently the haemorrhagic episodes occur in cycles in which there may be severe bleeding, yet the patient may be completely normal during the inactive phases (Estren, Médal, and Dameshek, 1946). The type of bleeding is dissimilar to that of haemophilia, and for that reason the name 'pseudohaemophilia' has been criticized (Biggs and Macfarlane, 1953), although haemarthroses have been reported. Strictly speaking it is likewise inaccurate to describe the bleeding as 'purpuric', as petechiae are rare, and occurred in only one of our patients. In other ways, however, such as a tendency to superficial bruising and bleeding from the mucous membranes, true purpura is simulated.

Traumatic bleeding is important, and includes haemorrhage following surgical operations and dental extractions. Such bleeding is, however, inconstant, and Estren, Médal, and Dameshek (1946) pointed out that haemorrhage may be severe after one operation and in no way excessive after another. Thus Minot (1928) reported two patients, one of whom had a decompression operation for a fractured skull, and the other a herniorrhaphy, without undue loss of blood. On the other hand, Little and Ayres's (1928) patient died from peritoneal haemorrhage following a splenectomy, and severe haemorrhage caused an abdominal operation to be abandoned in one of the patients reported by Estren, Médal, and Dameshek. In our series excessive bleeding on injury, including surgical trauma, was the commonest feature. Most of the patients bled excessively from cuts and scratches, and the men found it more convenient to shave at night because of the haemorrhage that invariably followed. Other traumatic episodes among our patients included profuse haemorrhage from a cut lip, and a severe contusion of the leg (due to a kick from a horse) which bled through the skin for several days. The behaviour of our patients after surgical operations was as unpredictable as Estren, Médal, and Dameshek have indicated. When one patient was submitted to a laparotomy because of repeated gastrointestinal haemorrhage, a partial gastrectomy was successfully performed, and another patient underwent removal of nasal polypi without excessive haemorrhage. On the other hand, one woman bled heavily from an antral operation and a mastoidectomy, and later from an appendicectomy. A partial gastrectomy was attempted on account of her repeated haematemeses, but there was continued oozing from the wound edges, and haematomata formed in the viscera when handled. The operation was abandoned, and she subsequently developed a blood-stained pleural effusion. Another patient had heavy bleeding from tonsillectomy and adenoidectomy, but appendicectomy later did not give rise to anxiety. Conization of the cervix and subsequent hysterectomy produced alarming haemorrhage in a woman whose chief symptom had been menorrhagia. Dental extractions seem to be a special hazard, yet here again excessive bleeding was not constant. Of our 20 patients, 14 had at some time or other bled severely after dental extraction. Transfusion was required in one, and many others had

to return to have the sockets packed or the gum sutured. Again, haemorrhage following dental extraction varies a great deal in severity in the same patient. Bruising, whether spontaneous or provoked, occurred in 15 of our patients. Many were found to have ecchymoses at the time of examination, and they frequently complained of bruising at the least knock.

Spontaneous haemorrhage occurs most often from the nose. Haemorrhage is also frequent from the gums, and in the form of menorrhagia. Less common is bleeding from the alimentary tract, urinary tract, respiratory tract, and into the brain and retina. Epistaxis occurred in 14 of our patients. Occasionally it was exsanguinating and required urgent blood transfusion. In Case 8 ligature of the ethmoidal arteries was contemplated, but fortunately did not prove necessary. Menorrhagia was complained of by nine of the 11 female patients over the age of 12 years. It was sufficiently severe in two of them to necessitate hysterectomy. Post-partum haemorrhage does not seem to have occurred invariably in those patients who had given birth. One woman (Case 6), when delivered of her first baby, did not lose an excessive amount of blood, in spite of an episiotomy, but on her second confinement she bled severely, and a transfusion had to be given. Another woman (Case 17) had eight confinements, and bled severely with each; her daughter bled severely in only two of her four confinements. The patient reported by Kotz, Kaufman, Hageage, and Garfinkle (1950) bled profusely from an episiotomy wound and cervical lacerations, and when a hysterectomy was ultimately performed severe bleeding occurred from the operation wound.

Gastrointestinal bleeding occurred in 10 of our 20 patients. This is a high incidence compared with the larger published series, but in some cases the source of haemorrhage was probably the nose. In Case 12 melaena occurred repeatedly from adolescence onwards, and at 48 years of age the patient complained of pain with the periodicity typical of peptic ulcer; an ulcer and a diverticulum were demonstrable in the duodenum on barium-meal examination. No source of haemorrhage was demonstrable in two patients (Cases 9 and 16), both of whom had severe episodes of gastrointestinal bleeding; the findings after a barium meal were negative. Bleeding from the gums, spontaneous or on brushing the teeth, occurred in five patients. Only one patient had true purpura, in the form of a few petechiae over the shoulders. There were four patients who complained of haematuria. In three it was an isolated event, but in the other it was the predominant symptom, and had been for many years. It was also the predominant symptom among her relatives. Cystoscopy revealed numerous small haemorrhagic areas on the vesical mucosa, from which blood could be seen trickling into the bladder cavity. Haemoptyses occurred in one patient, and were an annual event for a period of 14 years; no lesion was demonstrable on chest X-ray or bronchography.

Haemorrhage into joints in hereditary capillary purpura is of great interest, for it shows that this symptom is not confined to disorders of blood coagulation. Numerous examples have been reported (Rosenfeld, 1921; Little and Ayres, 1928; von Willebrand, 1931; Weeks, 1934; Bruun, 1939; Perkins, 1946; Halli-

well and Brigham, 1948; Cazal and Izarn, 1950; Zakhajm-Linget and Guigner, 1952). Buchanan and Leavell (1956) put the incidence of haemarthrosis at 8·5 per cent. of all published cases. One of our patients had haemarthroses affecting the right knee and right elbow; but haemophilia was never completely excluded, in spite of his prolonged bleeding time (17 minutes) and near-normal clotting time.

Laboratory Findings

In all cases the platelet count was above 120,000 per cu.mm. The bleeding time, measured by either the Duke or the Ivy method, was over six minutes in all but the two patients mentioned on page 175. In some the increase was only moderate, such as nine and a half minutes in Case 5 and seven minutes in Case 2, while in others it was 15 minutes or over. Estren, Médal, and Dameshek (1946), while stressing the variability of the bleeding time from patient to patient and at different times in the same patient, stated that in many instances the bleeding continued unabated from the site of puncture for hours. Such was the case with a family who had to break their journey home to seek first aid because of prolonged haemorrhage from their puncture wounds. The coagulation time was normal in 17 of the 18 patients in whom it was estimated. One (Case 14) had a venous clotting time which on occasions was on or just above the upper limit of normal, namely 11 to 13 minutes. Both Estren, Médal, and Dameshek (1946) and Revol, Favre-Gilly, and Ollagnier (1950) found examples in the literature of slight prolongation of the coagulation time. Capillary fragility, as judged by the tourniquet test, is variable in this condition. Von Willebrand originally reported a positive tourniquet test in his patients, but it was positive in only 54·3 per cent. of the cases reviewed by Buchanan and Leavell (1956). It was positive in seven out of 18 of our patients, and varied from time to time in the same patient.

The abnormal appearance of the nail-bed capillaries in this condition, and their inability to contract adequately on puncture, were described by Macfarlane (1941). This finding has since been confirmed by Levy (1947), Perkins (1946), Estren, Médal, and Dameshek (1946), and Cazal and Izarn (1950). O'Brien (1950) stated that tortuous capillaries, though occasionally found in a normal subject, were more numerous and more irregular in patients suffering from von Willebrand's disease. In seven of our patients the nail-bed capillaries were examined by Dr. Macfarlane or one of his colleagues, and five showed the typical abnormalities. O'Brien drew attention to the similarities of von Willebrand's disease, which he called 'diffuse capillary telangiectasia', and hereditary haemorrhagic telangiectasia. He emphasized a similar inheritance and clinical history, a similar capillary structure, the failure of the capillaries to contract on puncture, and the occurrence of the two conditions simultaneously in the same patient. One of our patients demonstrated this association:

Case 8. This female child, aged two years and eight months, was born of a consanguineous marriage, and a bleeding tendency was present on both sides

of the family. She had a tendency to bleed from birth, and had bled from the umbilical cord. She bruised easily, and had exsanguinating epistaxes for which she was frequently admitted to hospital for blood transfusion. Her bleeding time had been over 29 minutes, and capillary microscopy showed the changes characteristic of von Willebrand's disease. In addition, however, she had telangiectases on the face.

Hereditary Thrombocytopathic Purpura (Glanzmann's Disease)

The name 'hereditary haemorrhagic thrombasthenia' was given by Glanzmann in 1918 to a condition resembling thrombocytopenic purpura clinically, but in which the platelets were numerically normal. There was evidence of platelet malfunction in that clot retraction was impaired and the platelets appeared abnormal on the blood film. We have already indicated that the term thrombasthenia is too vague and should be abandoned in favour of thrombocytopathic purpura, as recommended in the Standard Nomenclature of Diseases and Operations. Further examples of functional insufficiency of the platelets have been published. Fonio (1930) reported a child of four years, in whom the bleeding time was prolonged and clot retraction impaired. The platelets, although numerically normal, were of large size and had fewer granules and some vacuoles, and there was absence of clumping. Similar findings in another patient were reported by Kugelmass (1932). Fonio described a further example in 1947 but, although the platelets showed gross abnormalities, the bleeding time, clot retraction, and tourniquet test were normal, and the coagulation time was prolonged. Languillon (1951) reported a girl who came from a family of bleeders, and who had a prolonged bleeding time, increased capillary fragility, and morphologically abnormal platelets. Clot retraction and prothrombin consumption were both impaired. Five patients with thrombocytopathic purpura have been reported by Revol under the name of *diacyclothrombopathie* (Revol, 1944; Guichard and Revol, 1949; Revol, 1954). They had prolonged bleeding times and poor clot retraction. There is evidence to show that the qualitative defect in the platelets may not be total, but may separately affect either the thromboplastic functions or those concerned with clot retraction. Bernard and Soulier (1948) described a boy with a prolonged bleeding time and normal platelet count; prothrombin consumption was poor, although clot retraction was normal. Similar results in another patient were reported by Debré, Bernard, Soulier, Buhot, Beaumont, and Lagrue (1952). Three of the patients reported by Jackson, Hartmann, and Conley (1953) also fall into this category. On the other hand, examples have occurred in which prothrombin consumption was normal and clot retraction impaired (Gautier and Guinand-Doniol, 1952; Jackson, Hartmann, and Conley, 1953; de Vries, Shafrir, Efrati, and Shamir, 1953; Bernard, Buhot, Beaumont, and Larrieu, 1954). In none of the Radcliffe Infirmary patients was there conclusive evidence of a functional platelet abnormality. The prothrombin consumption was normal in 10 of the 11 patients in whom it was tested (the poor prothrombin consumption in Case 20 being due to the deficiency of a clotting factor), and

the result of the thromboplastin generation test on the platelets was normal in seven patients. Clot retraction was tested in 13 patients and, if the lower limit of normal is taken as 44 per cent. of serum expressed in one hour (Macfarlane, 1939), 10 gave normal results. In Case 5 the result was 30 per cent. but all other affected members of the patient's family had a normal clot retraction, and Cases 13 and 17 gave a result of 40 per cent., which can be described as borderline. Soulier and Larrieu (1954) investigated 65 patients with a haemorrhagic syndrome associated with a prolonged bleeding time and normal platelet count. Clot retraction was deficient in four, and six out of 32 patients had an abnormal prothrombin consumption. This gives some indication of the incidence of proved thrombocytopathic purpura among patients with hereditary purpura.

Prognosis and Treatment of Hereditary Capillary Purpura

It is generally reported that the haemorrhagic tendency lessens with age, and this is also our clinical impression. Treatment is largely prophylactic, in the avoidance of trauma, and of surgical interference unless it is sufficiently urgent to warrant the risk. Dental extraction should be carried out in hospital. Transfusion during excessive bleeding replaces blood lost and counteracts shock; as there is no defect of coagulation in uncomplicated cases, there is no question of restoring any missing factor to the circulating blood, and no necessity for using fresh blood or plasma. Local pressure ought to be of help in producing ischaemia and allowing the blood time to coagulate. Splenectomy is of no value, and carries the risk of an abdominal operation in a patient with a haemorrhagic disorder (Giffin, 1928; Little and Ayres, 1928; Jackson, Hartmann, and Conley, 1953). One patient (Case 20) had a splenectomy performed elsewhere, with a suggestion of improvement.

Jacobson (1953) studied the effect of corticotrophin and cortisone on 18 patients with a prolonged bleeding time, among whom were six with a positive family history. In every instance but one treatment was followed by a fall in bleeding time and prevention or cessation of haemorrhage, so that some patients were able to undergo major surgery without mishap. This improvement, however, as stated earlier, can occur spontaneously in von Willebrand's disease. Corticotrophin produced some improvement in one of the patients of de Vries, Shafrir, Efrati, and Shamir (1953), but cortisone was ineffective in a patient of Debré, Bernard, Soulier, Buhot, Beaumont, and Lagrue (1952); both these patients had evidence of a functional platelet defect.

Case 15. This patient, a woman aged 31, had always bled and bruised easily, and had bled severely from dental extractions, although not abnormally from an appendicectomy. She was admitted on numerous occasions to the Department of Gynaecology and Obstetrics because of menorrhagia, and conization of the cervix led to severe bleeding, necessitating transfusion and resuture. When hormonal treatment was instituted she had bled intermittently for six months, during which time she could not remember going for longer than four days without loss of blood. She was given corticotrophin intramuscularly, 100 mg. daily for 20 days, making a total of 2 g. The bleeding time was

unaltered throughout (seven to 15 minutes). Bleeding ceased on the 11th day of treatment, only to start again when the hormone was withdrawn. It was not thought that corticotrophin brought about any appreciable change in this patient, and she was eventually subjected to a hysterectomy, which she survived in spite of severe haemorrhage.

The Association of von Willebrand's Disease with a Defect of Blood Coagulation

A number of patients have recently been reported as suffering from more than one abnormality of the haemostatic process. Alexander and Goldstein (1953) described two patients with 'pseudohaemophilia' (von Willebrand's disease) who were also found to have a deficiency of antihaemophilic globulin. A capillary defect was confirmed by a prolonged bleeding time and an abnormal microscopic appearance. Larrieu and Soulier (1953) reported a similar patient, a girl of six years. Her bleeding time was prolonged—in fact she bled all night from the puncture—and antihaemophilic globulin was found to be deficient by the thromboplastin generation test. Further examples of a deficiency of antihaemophilic globulin in patients with von Willebrand's disease have been described by Quick and Hussey (1953), Verstraete and Vandenbroucke (1955), Ingram (1956), and Schulman, Smith, Erlandson, Fort, and Lee (1956). Murphy and Clark (1944) reported the occurrence in the same patient of hereditary capillary defect (as indicated by a prolonged bleeding time and abnormal microscopic appearances) and a prolonged one-stage prothrombin time. As the prothrombin time was not corrected by the addition of normal plasma adsorbed with aluminium hydroxide, the missing factor could have been prothrombin or factor VII. A dual haemostatic defect was detected in one of our patients.

Case 20. A Polish girl was first admitted to the Children's Department in 1948 when nine years old. She suffered from bleeding gums, and from bruising and bleeding easily. Her sister died from haemorrhage after the incision of an abscess, and her father bled severely from shaving cuts, although unfortunately he was in Poland and not available for examination. She was mentally defective. Investigation in 1948 revealed a very prolonged bleeding time; there was no sign of cessation after 15 minutes. Her platelet count and one-stage prothrombin time were normal. The clotting time was normal (five minutes), but prothrombin consumption was markedly deficient (100 per cent. activity in the serum after one hour), although clot retraction was normal. Between 1948 and 1954 she was investigated in many hospitals, and in one had had her spleen removed. This operation produced a little symptomatic improvement, in that bleeding episodes became less severe and less frequent. Her most recent admission in 1954, at the age of 14, was for an attack of bronchopneumonia following an upper respiratory infection. She bled severely from the gums, and inhaled blood into her respiratory passages, requiring suction. Her gums were hypertrophied, resembling a case of monocytic leukaemia, and they bled on mild trauma.

She was further investigated by Dr. Rosemary Biggs. Evidence of a capillary defect was forthcoming, in that the bleeding time was over 15 minutes and the tourniquet test positive. The platelet count was 222,000 per cu.mm. The clotting time (Lee and White) was seven and a half minutes, and prothrombin

time normal (25·5 seconds compared with a control of 23 seconds). Platelet function was found to be normal with the thromboplastin generation test, but there was a complete absence of antihaemophilic globulin.

Discussion

The classification of the various hereditary haemorrhagic disorders can be related to the twofold concept of the haemostatic mechanism. The first stage of haemostasis depends upon the contraction of the capillaries, and defects of this process are to be found in hereditary telangiectasia and hereditary capillary purpura. Defects of the second stage, the coagulation of the blood, are more numerous, the commonest being haemophilia, together with Christmas disease from which it is clinically indistinguishable. The clinical features of haemophilia are as a rule so pathognomonic that there is little difficulty in distinguishing it from other forms of haemorrhagic disorder. The sex-linked recessive inheritance, the almost exclusive occurrence in male subjects, and the complaints of excessive bruising and bleeding, haemarthroses, and deep tissue haemorrhage, present a characteristic picture, while laboratory confirmation is to be found in a prolonged coagulation time and defective prothrombin consumption and thromboplastin generation.

Hereditary capillary purpura, which forms the subject of this paper, likewise has distinctive clinical features. The capillary abnormality is generalized, and gives rise to the characteristic finding of a prolonged bleeding time. It thus differs from the allied condition, hereditary telangiectasia, in which the vascular lesion is localized in discrete lesions frequently visible in the skin. The two conditions, however, have been known to coexist in the same patient. The irregular capillaries and their abnormal response to puncture have been observed microscopically. The disease is inherited most commonly as an autosomal dominant, although other patterns of inheritance have been reported. The characteristic clinical features are bleeding and superficial bruising on trivial injury, epistaxis, menorrhagia, and bleeding from the gums and other mucous membranes. The occurrence in female as well as male subjects, the frequency of epistaxis and other bleeding from mucosae, and the capricious behaviour and less lethal quality of the haemorrhagic tendency, all serve to distinguish it from haemophilia. Rarely a qualitative platelet disorder may be demonstrable in patients with hereditary purpura, forming the sub-group of hereditary thrombocytopathic purpura; this sub-group is associated with the name of Glanzmann. It can be diagnosed by defective clot retraction, prothrombin consumption, and thromboplastin generation, in spite of a normal number of platelets. Although haemophilia and hereditary capillary purpura can be so clearly distinguished, we have mentioned the occurrence of cases in which hereditary capillary purpura is combined with a deficiency of antihaemophilic globulin. The meaning of this conjunction is at present obscure. It may be due to a common hereditary background. On the other hand, there may be mild variants of haemophilia and hereditary capillary purpura which are recognized only when they come together.

This work would have been impossible without the help of Dr. R. G. Macfarlane and Dr. Rosemary Biggs, who carried out many of the laboratory investigations. We are also indebted to several colleagues who referred patients to us and allowed us to quote from their case records. The work was in part supported by a grant for expenses to one of us (L. J. W.) from the Medical Research Council.

Note. Since this paper was written I. M. Nilsson, M. Blomback, E. Jorpes, B. Blomback, and S.-A. Johansson (*Acta med. scand.* 1957, *159*, 179) have reported that antihaemophilic globulin was decreased in 15 patients from Aaland affected with von Willebrand's disease, and it is probable that a decrease of antihaemophilic globulin is more universal in von Willebrand's disease than we had realized.

Summary

1. The common forms of hereditary haemorrhagic disease are haemophilia (with which Christmas disease is included), hereditary capillary purpura, and hereditary capillary telangiectasia. Hereditary capillary purpura accounts for about one-quarter of all cases of hereditary haemorrhagic disease.

2. Hereditary capillary purpura (von Willebrand's disease) is associated with an abnormality in the structure and function of the capillaries, which results in a prolonged bleeding time. Much less frequently in hereditary purpura a disturbance in the functional efficiency of the platelets can be demonstrated, when the condition may be referred to as hereditary thrombocytopathic purpura or Glanzmann's disease. There are also cases of hereditary thrombocytopenic purpura. In rare cases hereditary capillary purpura may be combined with a deficiency of one of the clotting factors, notably antihaemophilic globulin.

3. The terms 'thrombasthenia' and 'pseudohaemophilia' are ill-defined, and should be avoided in classifying the hereditary haemorrhagic diseases.

4. Twenty patients with hereditary capillary purpura were seen between 1937 and 1954. One of them also had an absence of antihaemophilic globulin. The clinical picture, diagnosis, and hereditary pattern are discussed, and the literature reviewed.

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CONGENITAL AND ACQUIRED AGAMMAGLOBULINAEMIA[1]

A Report of Four Cases

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With Plates 20 to 23

Studies of congenital deficiencies have yielded valuable information on the biochemistry and function of many processes in the human organism. This has been especially true of the study of protein function and metabolism, and the recent advances in the field of blood coagulation, for example, owe much to the investigation of patients with congenital deficiencies of specific protein factors. The discovery of congenital and, to a lesser degree, acquired agammaglobulinaemia has been of special interest and importance to all those interested in the problems of protein metabolism, immunity, and antibody synthesis. Congenital agammaglobulinaemia was first described by Bruton in 1952, in a boy who had had many recurrent pneumococcal infections. No gamma globulin could be demonstrated by electrophoretic analysis in his serum, a normal antibody response could not be induced with standard antigens (for example, diphtheria toxoid), and he could be maintained free from infection by monthly injections of gamma globulins. Subsequently patients with both congenital and acquired agammaglobulinaemia have been reported with similar findings (Tables I and II). Four patients with very low concentrations of serum gamma globulin are reported in the present paper: a child probably with an acquired disorder, an adult with multiple myeloma, an adult with prolonged hypoproteinaemia and follicular lymphoblastoma, and a child with associated leucopenia and leg ulcers.

Case 1. A. T., a boy aged 14 years at the time of admission, had normal parents, and one sister aged three years who had presented feeding problems as a baby and at the age of five months had had one attack of pneumonia responding adequately to penicillin. There was no other relevant family history. The patient had progressed normally until the age of three and a half years, when he had his first attack of left-sided pneumonia; after this he had mumps, 'measles' on four occasions, two abscesses of the neck, infective hepatitis, and in the six months prior to admission five attacks of pleurisy and pneumonia. He had had recurrent bronchitis from the age of 10, and between the recent attacks of pneumonia he had coughed up a thick sputum, mainly in the mornings. Three days before admission he had had an attack of severe left pleural pain; it increased the next morning, and he began to cough up blood-stained sputum.

[1] Received June 3, 1957.

TABLE I

Congenital Agammaglobulinaemia

Number of patients	*Authors*	*History of onset at age (approx., years)*	*Sex*	*History of infection*	*Leucocyte response to infection*	*Response to treatment with gamma globulin*	*Response to treatment with antibiotics*	*Antibody formation: response to antigenic challenge*	*Isohaemagglutinin titre*	*Half-life of injected gamma globulin*	*Protein pattern in relatives*	*Steatorrhoea*	*Miscellaneous remarks*
1	Bruton (1952)	4½	M	+++	+++	+++	+++	–	..	..	..	..	3 bouts of mumps. Bone and liver biopies normal
3	Bruton, Apt, Gitlin, and Janeway (1952)	E.C.	M	+++	..	+++	+++	..	..	20 days in one patient	Normal	..	
9	Janeway, Apt, and Gitlin (1953)	E.C.	M	+++	+++	+++	+++	–	–	..	..	..	1 death; low gamma globulin in connective tissue
1	Jean (1953)	7	M	+++	+++	+++	..	..	..	..	..	..	
1*	Young, Wolfson, and Cohn (1955)	4	M	+++	+++	+++	..	..	–	40½ days	Minor abnormalities	..	Lymph-node: mild reticular-cell hyperplasia. Hepatomegaly and lymphadenopathy
3	Young, Wolfson, and Cohn (1955)	E.C.	M	+++	..	..	..	..	–	Normal	Normal	..	Lymph-node: diminished germinal centres and lymphocytes in general
1	Hutchison (1955)	½	M	+++	–	–	–	Vaccinated at 4/12. No anti-bodies	Group O; low α and β titres	..	..	..	Died. Interstitial pneumonia with little tendency to fibrosis. Diarrhoea; stool culture negative
1	Hayles, Stickler, and McKenzie (1954)	½	M	+++	..	..	..	..	..	..	..	..	Died. Granulomatous lesions in liver; generalized anasarca
1	,, ,,	3	M	+++	–	±	+++	..	..	..	..	..	Normal vaccination at 1½ years old
1	,, ,,	1½	M	+++	+++	+++	+++	..	..	..	..	..	
1	,, ,,	½	M	+++	..	..	..	..	..	..	..	..	
1	Good and Mazzitello (1956)	½	M	+++	..	..	..	..	..	..	..	..	Siblings. No history of infection (the younger patient under treatment with γ-globulin)
1	,, ,,	½	M	..	..	+++	+++	..	..	..	..	..	
1	,, ,,	½	M	+++	Cyclic neutropenia	..	..	..	..	..	..	..	Siblings. Died aged 20/12 with respiratory infection
1	,, ,,	½	M	+++	Neutropenia	..	..	..	..	..	..	..	Siblings. Died with staphylococcal pneumonia
1	,, ,,	½	M	+++	..	..	..	..	..	..	..	..	
1	Moncke (1954)	3	M	+++	..	+++	+++	..	..	..	..	..	
1	Sanford, Favour, and Tribe-man (1954)	E.C.	F	+++	+++	..	..	..	–	..	2 sons normal	+++	Female. Vaccination E.C. apparently normal. Mantoux negative 1/100
30													

E.C. = Early childhood. ± = Good response to acute attacks; did not control long-term progress. * Classified by authors as non-lymphopenic agammaglobulinaemia of adults.

TABLE II

Primary Acquired Agammaglobulinaemia

Authors	*History of onset at age (approx., years)*	*Sex*	*History of infection*	*Lymph-node enlargement*	*Splenomegaly*	*Hypersplenism*	*Leucocyte response to infection*	*Response to treatment with γ-globulin*	*Response to treatment with antibiotics*	*Antibody formation: response to antigen challenge*	*Isohaemagglutin titre*	*Protein pattern in relatives*	*Steatorrhoea*	*Miscellaneous remarks*
Grant and Wallace (1954)	15	F	+	−	+	?	−	+	+	−	−	N	..	Congenital cataracts. Mantoux positive 1/100. Leucopenia. ? Hypersplenism
Zinneman, Hall, and Heiler (1954)	17	M	+	..	+	..	−	+	+	−	−	..	..	Group B; anti-A 1/8; no increase in titre on giving group A cells
,, ,,	29	M	+	..	+	..	±	..	+	−	−	..	..	
,, ,,	18	F	+	..	+	+	−	..	+	−	−	..	..	Leucopenia and arthralgia cured by splenectomy. Epithelioid-cell granuloma and absence of plasma cells throughout lymphatic tissue. ? Sarcoidosis
Lang, Schettler, and Wildhack (1954)	10	F	+	..	+	..	+	..	+	±	±	N	..	Plasma cells in marrow. Globulin half-life normal. Mantoux positive 1/100
Prasad and Koza (1954)	21	F	+	+	+	+	+	..	+	−	..	..	..	Hepatomegaly; granulomata in liver and spleen; pancytopenia cured by splenectomy. ? Sarcoidosis
Wall and Saslaw (1955)	26	M	+	..	..	..	+	..	+	−	±	N	..	Congenital mental defect, cleft palate, and dislocation of hip. Hepatomegaly
,, ,,	40	M	+	..	..	..	..	..	+	−	..	..	+	Lymph-node: reticulum-cell hyperplasia. Slow healing
Collins and Dudley (1955)	26	F	+	..	..	..	+	±	−	..	±	..	..	Died. Lymph-node: cortex poorly defined, no follicles, no plasma cells
,, ,,	50	F	+	..	+	..	−	..	−	..	..	N	..	Died. Lymph-node (as above)
Seltzer, Baron, and Toporek (1955)	19	M	+	+	+	..	+	+	+	−	−	..	?	Hepatomegaly. Normal γ-globulin half-life
Rohn, Behnke, and Bond (1955)	19	M	+	+	+	+	..	+	+	..	..	..	..	Lymph node: no plasma cells, few mature lymphocytes; burnt-out inflammation or granuloma. Pancytopenia cured by splenectomy
Rosecan, Trobaugh, and Danforth (1955)	49	M	+	..	+	..	−	±	+	..	−	..	+	No plasma cells in marrow. Normal complement level. Serum-protein half-life normal
,, ,,	33	M	−	..	+	..	?	..	..	..	−	..	?	Lymph-node: absent follicles. No plasma cells in marrow. Normal complement level
Brem and Morton (1955)	26	M	+	+	+	..	+	±	+	−	−	..	..	Repeated attacks of infectious hepatitis. Lymph-node follicles: hyperplasia
,, ,,	10	M	+	+	+	..	..	−	−	..	−	..	..	Died at 17 years with pneumonia. Lymph-node follicles: hyperplasia
,, ,,	6	M	+	+	+	..	..	+	..	..	−	..	..	Cirrhosis
,, ,,	21	M	..	..	..	..	..	..	..	?	±	..	..	No plasma cells in marrow
,, ,,	3	M	..	..	..	..	..	..	..	..	+	..	..	Originally hypoproteinaemia (Stern and Reiner, 1946). Only γ-globulin absent now
Good and Mazzitello (1956)	54	M	+	..	..	..	..	..	..	..	..	..	..	Large thymoma
,, ,,	22	F	+	+	+	+	+	..	+	..	..	..	..	Lymph-node: granulomata and proliferation of reticulum stroma. Anaemia and leucopenia cured by splenectomy
Martin, Gordon, and McCullough (1956)	56	F	+	+	+	?	−	−	+	±	−	..	..	Lymph-node: no germinal centres; plasma cells and reticulum cells rarely seen. Hepatomegaly
Wechsler and Wolf (1956)	48	F	+		+	..	±	+	+	−	−	..	..	Hepatomegaly

± = Some response, but not a complete one. N = Normal. ? = Possibly.

He vomited several times, and had several attacks of diarrhoea, but no abdominal pain. He became feverish and short of breath, and was very ill when admitted on 9.5.53.

Examination revealed a very pale, faintly cyanotic boy, with a respiratory rate of 40 per minute, a pulse-rate of 140 per minute, and a temperature of 103° F. Clubbing of his fingers was present, and the classical signs of consolidation were elicited at the left base posteriorly. His spleen was palpable 8 cm. below the costal margin. A chest X-ray confirmed the clinical findings of consolidation, and a provisional diagnosis was made of left-lower-lobe pneumonia related to bronchiectasis. He responded very rapidly to 500,000 units of penicillin eight-hourly, and two days later a chest X-ray report read 'There is evidence of recent pneumonitis in the left mid-zone, and lung markings are also increased at the right base' (Dr. M. J. Edwards).

On 11.8.53 his haemoglobin was 11·0 g. per 100 ml., platelets 206,000 per cu. mm., and total white-cell count 3,600 per cu. mm. (neutrophils 1,368 (38 per cent.), lymphocytes 1,728 (48 per cent.), monocytes 486 (13·5 per cent.), basophils 18 (0·5 per cent.)). The prothrombin index was 100 per cent., serum-bilirubin 0·2 mg. per 100 ml., serum alkaline phosphatase 9 King-Armstrong units, and the thymol turbidity test negative. The stool was watery, and contained undigested food particles and mucus; microscopic examination was reported as showing 'blood and leucocytes moderate; mucus profuse; faecal debris profuse; undigested meat-fibres moderate; fatty acid crystals occasionally; no cysts, amoebae, or ova'. A culture grew *Bact. coli*, *Proteus vulgaris*, and *Strep. faecalis*. No gamma globulin was detected in the patient's serum by paper electrophoresis (Table III).

He was transferred to the Clinical Research Unit for special studies on 4.6.53. During his first three weeks in the ward he was well, apart from several bouts of unexplained pyrexia. On 24.6.53, after an injection for cholera immunization, he became ill and developed fever, vomiting, and diarrhoea. He was treated with penicillin and chloramphenicol, but his blood-pressure fell to 60/30, and his pulse-rate rose to 160. At this stage he was clinically dehydrated. His blood-pressure was maintained with noradrenaline in normal saline, but he developed signs of pulmonary oedema, and died.

Autopsy findings (Dr. V. J. McGovern, Histopathologist, Fairfax Institute of Pathology). *Lymphatic tissue.* The thymus was slightly enlarged, and the lymph-nodes showed reactive hyperplasia, while the germinal centres in the spleen were prominent. The lymphoid tissue in the alimentary tract was hyperplastic, the change being most marked in the duodenum and jejunum (Plate 20, Fig. 1 *a* and *b*). Germinal centres were prominent in the lymphoid follicles, but no plasma cells could be detected. Occasional plasma cells could be detected in the lamina propria of the intestine, but these were less numerous than in normal subjects. *Bone-marrow.* There was very active erythropoiesis in the sternum and vertebrae and, while plasma cells could be seen, they were not numerous. *Liver.* The architecture was normal, but the sinuses contained fairly numerous leucocytes. *Suprarenal glands.* There was an extensive haemorrhage into the cortex of each suprarenal gland. *Lungs.* Pleural adhesions obliterated both pleural cavities. There were numerous small petechiae on the pleural surfaces of each lung, and bronchiectasis was present in the left lower lobe and lingula. The right upper and lower lobes were collapsed, and there was slight oedema of the right middle lobe.

Case 2. A. H. K., a 53-year-old man admitted on 19.8.56, had first noticed a low backache in 1949; it slowly increased in severity, and in 1952 he also

noticed pain in the chest, which was aggravated by movement or coughing. There were no other relevant symptoms. On physical examination his blood-pressure was 180/100, and there was local tenderness to pressure over the spines of vertebrae T4, T5, and T12; the liver and spleen were not palpable, and there were no other abnormal findings. Urinary examination revealed Bence-Jones proteose, but no other abnormality. An X-ray of the chest and spine showed a compression fracture of the body of vertebra T7, with a wedge deformity, and slight compression of the bodies of L1 and L2. The ribs showed no definite lesion, although one part of the left 12th rib seemed irregular and expanded. The haemoglobin was 14·7 g. per 100 ml., the haematocrit level 40 per cent., red-cell count 4,600,000 per cu. mm., mean corpuscular volume 86 cu. μ, mean corpuscular haemoglobin 31 μg., mean corpuscular haemoglobin concentration 36 per cent., and colour index 1·06. The erythrocyte sedimentation rate was 2 mm. in one hour (Hawksley). The total white-cell count was 4,400 per cu. mm. (neutrophils 2,508 (57 per cent.), lymphocytes 1,584 (36 per cent.), monocytes 220 (5 per cent.), and eosinophils 88 (2 per cent.)); no plasma cells were seen in the peripheral blood. Bone-marrow biopsy showed an abnormally high plasma-cell count, suggesting myelomatosis. The serum-phosphate was 5·8 mg. per 100 ml., serum-calcium 11·2 mg. per 100 ml., serum alkaline phosphatase 12·8 King-Armstrong units, serum acid phosphatase 2·1 King-Armstrong units, and serum-protein 6·1 g. (albumin 4·0 g.) per 100 ml. An electrophoretic pattern appeared normal apart from a complete absence of the gamma-globulin component (Plate 23, Fig. 7*b*), but detailed analysis revealed an increase in the beta globulin (Table III).

He was discharged on 3.9.52 in a plaster jacket, which had relieved his back pain, but his condition slowly deteriorated, and the pain in the chest caused him increasing trouble. On 10.11.54 an X-ray report of the thoracic and lumbar vertebrae read 'There is extensive destruction of the lower thoracic vertebral bodies, less marked in the mid-thoracic and upper lumbar regions. There is considerable erosion with some expansion in the majority of ribs, especially the lower ones, and there are large areas of erosion in both iliac bones' (Dr. G. M. Potts). At this time his serum total protein was 5·3 per 100 ml., and his blood-urea was 37 mg. per 100 ml. He deteriorated further, but was not seen after 21.12.54.

Case 3. J. S., when aged 23 years, developed bilateral axillary lymphadenopathy, and biopsy showed the presence of follicular lymphoblastoma. Eight months later he was admitted to another hospital with splenomegaly, lymphadenopathy, and anasarca. He had a mild anaemia (haemoglobin 9·5 to 11·5 g. per 100 ml.), and a persistent leucopenia; the maximum white-cell count was 2,800 per cu. mm., with an essentially normal distribution. He was given X-ray therapy, and referred to Royal Prince Alfred Hospital.

On admission on 25.8.51 he had gross splenomegaly, cervical, axillary, and inguinal lymphadenopathy, hepatomegaly, ascites, and oedema of the lower limbs to the thighs. Paracentesis abdominis on each of two occasions yielded four litres of blood-stained fluid. A biopsy of his axillary nodes confirmed the earlier report. He was discharged virtually free of oedema after treatment with a low-salt diet and mersalyl. During the next three and a half years he had several applications of deep X-ray therapy to various lymph-node masses, with rapid responses. A course of triethylene melamine, commenced on 18.6.53, was followed by mild anasarca, and a month later, while still taking triethylene melamine, he began to vomit and to have diarrhoea. This diarrhoea persisted with remissions and exacerbations throughout the remainder of his illness.

He was readmitted for investigation on 18.8.53, and his total serum-protein was found to be 3·0 g. per 100 ml. (Kjeldahl) (albumin 2·1 g. per 100 ml.); the blood urea nitrogen was 11 mg. per 100 ml., serum-cholesterol 88 mg. per 100 ml., thymol turbidity 0, zinc sulphate turbidity 0, and prothrombin index 84 per cent. The haemoglobin was 14·7 g. per 100 ml., platelet count 30,000 per cu. mm., and total white-cell count 1,700 per cu. mm. (neutrophils 1,122 (66 per cent.), lymphocytes 476 (28 per cent.), monocytes 68 (4 per cent.), eosinophils 17 (1 per cent.), and basophils 17 (1 per cent.)). A paper electrophoretic pattern of his serum showed a marked reduction of albumin and gamma globulin, with a relative increase of alpha and beta globulins, but the pattern did not resemble that of a nephrosis or cirrhosis. He had no albuminuria. Another axillary lymph-node biopsy was performed, and the report read 'The appearance is that of follicular lymphoblastoma, and in places the lymph-node architecture has been destroyed. This suggests transformation to lymphosarcoma' (Dr. V. J. McGovern) (Plate 21, Fig. 2). A liver biopsy was performed, and the report read 'In the portal tracts there is proliferation of the reticulum cells and primitive lymphoid cells. This is a further step in the progression of follicular lymphoblastoma' (Dr. V. J. McGovern) (Plate 21, Fig. 3). The generalized oedema was once again controlled with a low-salt, high-protein diet and mersalyl injections, and he was discharged on this regimen and given weekly testosterone injections.

On 8.10.53 he was readmitted with a mild cellulitis of his right thigh, after a bout of vomiting, diarrhoea, and tetany. The following values were found in the serum: sodium 135 m-equiv., potassium 3·5 m-equiv., CO_2 combining power 25·5 m-equiv., and chloride 112 m-equiv. per litre; calcium 6 mg. and phosphorus 5·8 mg. per 100 ml.; alkaline phosphatase 6·3 King-Armstrong units, and acid phosphatase 1·6 King-Armstrong unit. His general condition improved rapidly with treatment, and after the administration of deep X-rays to his right iliac fossa there was a rise in the total serum-protein concentration from 2·2 g. per 100 ml. (albumin 1·2 g.) to 5·7 g. per 100 ml. (albumin 3·5 g.) in three weeks. This level was not sustained, however, and in two weeks had fallen to 4·8 g. per 100 ml. A routine four-day fat balance revealed that on an intake of 90 g. of fat per day his stools contained 9·8 g. of fat per day. His spleen was still enlarged, and the serum-protein values and blood count were unchanged. It was thought that his diarrhoea might have been due to involvement of his small bowel and mesenteric glands, and a course of deep X-rays to his abdomen was begun, but had to be discontinued owing to nausea and vomiting. On 25.6.54 he had another course of X-rays to the mesenteric nodes, leading to severe reactions, but to no response in the serum-proteins. He was given courses of corticotrophin and cortisone in 1953 and 1954, which improved him symptomatically but had no effect on his serum-proteins or blood count. Nearly six years after his first symptoms he had his most severe attack of diarrhoea, and bouts of vomiting, which forced him to cease work, and for the first time he began to lose weight. For six weeks he had weekly intravenous infusions of 25 g. of salt-free albumin.

He was readmitted at the beginning of his sixth year of illness, and examination of his serum revealed sodium 137 m-equiv., potassium 4·0 m-equiv., CO_2 combining power 24·8 m-equiv., and chloride 109 m-equiv. per litre; cholesterol 120 mg. per 100 ml., and blood-urea 28 mg. per 100 ml.; the total serum-protein was 3·7 g. per 100 ml., thymol turbidity 0·5 unit, zinc sulphate turbidity 1·2 unit, serum-calcium 8·2 mg. per 100 ml., serum-phosphorus 4·3 mg. per 100 ml., serum-bilirubin (1′) 0·05 mg. and (15′) 0·4 mg. per 100 ml., and serum alkaline phosphatase 10·0 King-Armstrong units; the Mantoux reaction was negative at

1/100. A stool culture was negative. An electrophoretic pattern showed a markedly reduced albumin level, an absent gamma-globulin fraction, increased $alpha_1$ and $alpha_2$ fractions, and a normal beta-globulin fraction (Plate 23, Fig. 7*d*, and Table III). X-ray examination of the small bowel showed 'disordered motor function, especially in the ileum, with flocculation and fragmentation' (Dr. A. R. Colwell). Since similar X-ray pictures had been seen in one of our patients with localized ileitis associated with steatorrhoea and vomiting, it was decided to perform a laparotomy after preparation with daily infusions of albumin. Laparotomy disclosed a diffuse erythema of the small bowel, especially marked in the terminal ileum, in the caecum, and in the colon as far as the commencement of the descending colon. A biopsy of the wall of the caecum showed non-specific typhlitis. After the operation the patient's diarrhoea settled down, and he felt improved. He was discharged, but soon relapsed, with nausea, vomiting, and colicky pains in the abdomen. In spite of various therapeutic measures he became much worse, and was readmitted; but all efforts at nutrition failed, and he died four days later, aged 29½ years.

Autopsy findings (Dr. V. J. McGovern). *Lymph-nodes.* Most of the lymph-nodes showed changes due to irradiation. In one abdominal lymph-node there was a fairly uniform cellular appearance, although sinuses were still visible. The cells of the medulla were composed of lymphoblasts and very atypical lymphocytes, but plasma cells were present. None of the lymph-nodes resembled those examined in the biopsies. *Liver.* The architecture was normal. In some of the portal tracts there was infiltration, composed mainly of lymphocytes, but there were also a few polymorphs. These infiltrations were much less marked than at the time of the liver biopsy. *The small intestine* showed wasting of the muscle and thinning of the submucosa. There was slight inflammatory infiltration in the mucosa, particularly in the villi, composed of polymorphs and eosinophils, with a few histiocytes. Plasma cells were present in their usual numbers in the lamina propria (Plate 21, Fig. 4). *The spleen* was normal except for a little calcium deposit in its capsule.

Case 4. R. B. is a boy, aged 14 years in 1956. He has no significant family history, apart from a sister who died at seven weeks with pneumonia, and another sister, aged 12 years, who had frequent attacks of bronchitis until the age of 10. In 1942, when six weeks old, he had his first attack of bronchitis, and since then he has had many attacks with cough, sputum, and fever, and was thought to have bronchiectasis and sinusitis. He was treated energetically with sulphonamides in all the early episodes. In 1946 he was admitted to the Royal Alexandra Hospital for Children in one of his 'bronchitic' attacks, and chest X-rays were reported as showing 'changes at the left base, possibly bronchiectasis, possibly unresolved pneumonia'. The haemoglobin was 10·5 g. per 100 ml., and the white-cell count 2,100 per cu. mm. (neutrophils 525 (25 per cent.), lymphocytes 1,533 (73 per cent.), monocytes 42 (2 per cent.); no eosinophils or basophils). Sternal aspiration and biopsy was performed, and the report was as follows (Dr. R. D. K. Reye): '*Smear*: mature segmented polymorphs, metamyelocytes, and myelocytes are all present in excess of normal. There is no disturbance of the erythroid series. Mitotic figures are present, but they are not unduly numerous, and there is no increase in myeloblasts. A small number of myelocytes and a large number of polymorphs have vaculoated cytoplasm. *Section*: this confirms the aspiration. The marrow is cellular but not overpacked, and the architecture is normal. The excess of mature granular cells is very apparent in these preparations.' It was thought that the patient had developed granulocytopenia secondary to sulphonamide therapy. On his return home in

1946 it was noticed that ulcers were occurring frequently on his knees. These usually followed some minor trauma, were never pustular, and developed thin crusts; after healing, which often took at least a month, atrophic scars remained. It was also noticed that he did not heal as rapidly as his brother and sisters when he sustained a laceration.

In 1953 he knocked his left shin, and an ulcer appeared, which was still present when he was admitted on 4.4.56. In 1954 a similar ulcer appeared spontaneously on the outer side of his right leg (Plate 22, Fig. 5). In 1955 a Mantoux test was performed, and found to be negative; he was then inoculated with B.C.G., and developed a large sore. It healed slowly, and a circular scar, 2·5 cm. in diameter, still remains. He was referred by Dr. J. I. Loewenthal to the Clinical Research Unit for investigation of the nature of these ulcers.

The boy was found to be smaller than would be expected for his age and the stature of his parents (he was 159 cm. tall and weighed 49 kg.). On his left leg there was an ulcer, about 7·5 cm. × 5·0 cm., over the outer surface of the tibia, and on his right leg there was another, 12·5 cm. × 7·5 cm., over the lateral aspect. Many small 'tissue-paper'-like scars were concentrated around both knees. Peripheral pulses were readily palpable. A firm spleen was palpable 2 cm. below the left costal margin, and the liver was not palpable. There were no abnormal findings in the respiratory, cardiovascular, or nervous systems.

Laboratory investigations. The haemoglobin was 12·5 g. per 100 ml., and the white-cell count 1,100 per cu. mm. (neutrophils 220 (20 per cent.), lymphocytes 740 (67 per cent.), monocytes 120 (11 per cent.), and eosinophils 20 (2 per cent.)); the platelets were 284,000 per cu. mm.; the erythrocyte sedimentation rate (Wintrobe) was 8 mm. in one hour. The serum-bilirubin was $< 0{\cdot}2$ mg. per 100 ml., serum alkaline phosphatase 17 King-Armstrong units, thymol flocculation negative, and zinc sulphate turbidity 2 units; bromsulphthalein retention was 1 per cent. after 55 minutes. The blood-urea was 29 mg. per 100 ml., serum-cholesterol 140 mg. per 100 ml., serum uric acid 4·0 mg. per 100 ml., and serum-creatinine 0·8 mg. per 100 ml. A fat balance was performed, and there was a normal fat excretion of 1·75 g. per day on an intake of 90 g. of fat per day. Tiselius electrophoretic analysis of the serum did not show a gamma-globulin peak (Plate 23, Fig. 7*e*, and Table III). Paper electrophoresis, however, revealed a gamma-globulin component which was greatly reduced.

Special Investigations

Electrophoresis. The patients' sera were analysed by paper and moving-boundary electrophoresis. Paper electrophoresis was performed with Munktell 3 MM paper between siliconed glass plates, and a veronal/veronal buffer of pH 8·6 and ionic strength 0·05. The dried paper was stained with bromphenol blue. Detailed analysis of the serum-protein fractions in our first patient was performed by the dye-elution technique of Cremer and Tiselius (1949–50) (Table III). Moving-boundary electrophoresis was carried out by the classical Tiselius method, in a Perkin-Elmer apparatus incorporating a Philpot-Svenson optical system and Longworth's scanning method. Serum was diluted 1/4 with a veronal/veronal buffer at pH 8·6 and ionic strength 0·1, against which it was dialysed in the cold for 18 hours. Protein concentrations of the fractions were determined by measuring the areas beneath the pattern (Tiselius and Kabat, 1939) (Table III and Plate 23, Fig. 7).

Immunochemical studies. Ouchterlony's method (Oudin, 1952) of gel diffusion was employed to identify the gamma globulin in the patients' sera. Purified agar was made up to a concentration of 1·5 per cent. w/v in normal saline, merthiolate to a final concentration of 1/10,000 was added as a preservative, and the hot agar solution was poured into a Petri dish 9 cm. in diameter. Shallow cups were made in the agar, one in the centre, and up to six others equally spaced at a radius of 1 cm. from it (Plate 22, Fig. 6). Rabbit anti-human-gamma-globulin serum was prepared by injecting pooled human gamma globulin

TABLE III

Results of Serum Electrophoresis

Case number	Total protein (g./100 ml.)	Albumin (g./100 ml.)	Globulin (g./100 ml.)			
			Alpha$_1$	Alpha$_2$	Beta	Gamma
1*	5·5	3·1	0·6	0·9	0·9	..
2	4·7	3·3	0·7	0·9	1·5	..
3 (4.4.54)	3·9	2·4	0·4	0·5	0·5	0·1
(4.8.55)	3·6	1·4	0·8	0·7	0·7	..
4	6·3	4·2	0·4	0·6	1·1	..
5†	7·6	5·2	0·5	1·0	0·9	..

* Protein analysis by paper electrophoresis.
† Congenital agammaglobulinaemia (Lee and Tink, 1956).

(supplied by the Red Cross Blood Transfusion Service) into a rabbit, using the technique advised by Kabat and Mayer (1948). The prepared antiserum was shown to be specific for gamma globulin by setting up a plate with the antiserum in the central cup and, the fractions of normal serum (albumin, α_1-, α_2-, β-, and γ-globulin) individually placed in the surrounding cups. These fractions were obtained by electrophoretic separation of normal serum and elution of the appropriate paper strips with normal saline (Wunderly, Gloor, and Hässig, 1953). A precipitate formed only between the cups containing the gamma globulin and the central cup. This precipitate consisted of two closely spaced lines, which were shown in another plate to be identical with the two lines formed by normal serum diluted 1/100 (Oudin, 1952). In yet another plate (Plate 22, Fig. 6) the undiluted anti-human-gamma-globulin serum was placed in the central cup, and sera from each patient and a normal control were placed individually in the surrounding cups. The patients' sera were undiluted, whereas the normal serum was diluted 1/100 with normal saline. Fig. 6 shows that all four of our patients, and one patient with congenital agammaglobulinaemia (Lee and Tink, 1956), had immunologically detectable amounts of gamma globulin. The lines developed most rapidly and strongly between the central cup and that containing serum from Case 4. This patient, unlike the others, had sufficient gamma globulin in his serum to enable it to be detected electrophoretically. On the other hand, the lines developed last, and were the weakest, between the central cup and that containing serum from Case 2. This was thought to indicate that this patient's serum contained the least quantity of gamma globulin.

Antibody production. The response of three of our patients to antigenic stimulation was studied by Dr. E. F. Thomson, of the Fairfax Institute of Pathology,

and the results are shown in Table IV. Isohaemagglutinin titres were estimated by the Red Cross Blood Transfusion Service, and the results obtained are also shown in Table IV (Dr. R. J. Walsh).

TABLE IV

Immunological Tests

Case number	*Mantoux test*	*Schick test*	*Response to S. typhi H and O*	*Response to S. paratyphi B*	*Blood group*	*Isohaemagglutinin titre*	*Coombs test*	*Paul-Bunnell test*	*Cold agglutinins*
1	−	+	−	+	B−	Anti-A_1 1/256 Anti-A_2 1/64	−	−	−
2	+ (1/1,000)	..	..	..	A−	..	..	..	..
3	− (1/100)	..	+	+	O +	..	−	−	−
4	+ (1/100)	−	+	+	A_2 +	Anti-B 1/16	−	−	−

Discussion

Classification

A satisfactory classification of the hypogammaglobulinaemic states cannot be made until much more is learnt about the mechanism of their production. It has been pointed out that the term agammaglobulinaemia has been incorrectly applied to many such patients (Gitlin, 1955*a*; Martin, Gordon, and McCullough, 1956), since gamma globulins have been demonstrated to be present in the sera of all but one patient (Gell, 1955) when immunochemical methods were used, and Young and Wolfson (1954) have emphasized the fact that $beta_2$ globulins are often lacking as well as gamma globulins. All of our patients were demonstrated to have some gamma globulins by immunological methods (Plate 23, Fig. 7), although in three of them none could be shown electrophoretically. We obtained similar results in another patient with congenital agammaglobulinaemia referred to us for investigation (Lee and Tink, 1956) (Table III; Plate 23, Fig. 7*f*). A diagnosis at present rests on a history of recurrent infections and the electrophoretic finding of an absent gamma-globulin fraction, and we consider that in such patients the term agammaglobulinaemia may be retained, to distinguish them from patients in whom the gamma-globulin fraction is markedly reduced but can still be detected electrophoretically, as is the case in our fourth patient. Table V presents our working classification, which we realize will have to be modified or completely changed in the future.

1. *Transient hypogammaglobulinaemia of infancy.* The synthesis of gamma globulin in the newborn may not begin for the first month, and during this time there is a gradual loss of the maternal gamma globulin which was transferred to

the foetus across the placental barrier. Normally the level drops in one month to one-third of the value at birth; it is then maintained for another two months, and then begins to rise gradually, so that the adult level is reached only at two years of age (Orlandini, Sass-Kortsak, and Ebbs, 1955). In some instances a low level of gamma globulin may persist for some months, and be associated with recurrent infections (Gitlin, 1955*a*). This condition may be termed transient hypogammaglobulinaemia of infancy. Gitlin (1955*b*) considered that a two-months-old baby girl, who died with generalized vaccinia and agammaglobulinaemia (Keidan, McCarthy, and Haworth, 1953) belonged to this category. The

TABLE V

Classification of the Hypogammaglobulinaemic States

1. Transient hypogammaglobulinaemia of infancy
2. Congenital agammaglobulinaemia
3. Primary acquired agammaglobulinaemia
4. Secondary acquired agammaglobulinaemia, due to (*a*) myeloma; (*b*) lymphoma (*c*) chronic lymphatic leukaemia
5. Hypogammaglobulinaemia
6. Hypogammaglobulinaemia associated with hypoproteinaemia
7. Hypogammaglobulinaemia associated with the familial dysproteinaemia of Homburger

autopsy findings differed considerably from those seen in congenital agammaglobulinaemia (see below), since plasma cells and monocytes were very numerous, although the lymphoid tissue was diminished in amount in both lymph-nodes and spleen.

Congenital agammaglobulinaemia. We consider a patient to have this condition when there is a history of recurrent infection since early childhood, no gamma globulin in the serum demonstrable by paper electrophoresis, no evidence of any disease known to cause the condition, and a normal half-life of gamma globulin when given by infusion. This wide definition may include several varieties of agammaglobulinaemia, but insufficient is known to justify a more elaborate classification at present. Rohn, Behnke, and Bond (1955) have divided this group into three sub-groups: (1) lymphopenic agammaglobulinaemia of infancy; (2) lymphopenic agammaglobulinaemia of adults, and (3) non-lymphopenic agammaglobulinaemia of adults. The first two divisions are probably artificial, because the adults may have the same condition as the children. Lymphopenia has been present in the majority of patients with congenital agammaglobulinaemia, but there have been a few exceptions (Hayles, Stickler, and McKenzie, 1954; Hutchison, 1955), although the white-cell counts in the latter instances were performed during infective episodes. The serum-protein patterns of the patients' parents and the microscopic examination of lymph-nodes were not reported, so that the question whether these patients are other examples of the non-lymphopenic agammaglobulinaemia reported in a single patient by Young, Wolfson, and Cohn (1955) cannot be elucidated. We have performed serum-protein analyses in the case of one patient with congenital agammaglobulinaemia (Lee and Tink, 1956), and he had a marked lymphopenia between bouts of infection. Microscopic examination of lymph-nodes in these

patients has revealed markedly diminished or absent germinal centres, a diminished number of lymphocytes, and a lack of plasma cells (Good, 1954; Young and Wolfson, 1954).

The chief features recorded in patients with congenital agammaglobulinaemia are summarized in Table I. It is unfortunate that few of them have had gamma-globulin half-life studies or the serum-protein analyses of their relatives reported. It will be noted that the last patient in Table I is a woman, the only female patient reported, and differed from the others only in that the infective episodes were less severe in her childhood. For the present she must be classified as having congenital agammaglobulinaemia.

Primary acquired agammaglobulinaemia. Under this heading we include those patients who have a history of recurrent infections commencing after early childhood, and no serum gamma globulin demonstrable by electrophoresis, and in whom no underlying cause can be demonstrated. The deficiency of immunoglobins is usually not as complete in these patients as in congenital agammaglobulinaemia, the gamma-globulin level is usually not as low (Gitlin, 1955*a*; Good and Mazzitello, 1956), the isohaemagglutinins may not be entirely absent, and there may be some antibody response to certain antigens (Table II). In none of the primary acquired cases was any specific cause apparent, although there seemed to be three groups in which many patients could be classified after examination of their lymph-nodes. These groups were those associated with (1) absence of germinal centres; (2) 'benign' follicular hyperplasia; (3) replacement of normal architecture by a granulomatous process.

We consider that this condition may represent a very mild form of reticulosis, a view that is supported by the frequency of splenomegaly and lymphadenopathy, and hence the division of acquired agammaglobulinaemia into primary and secondary may be unreal. It is interesting, in this respect, that three cases described by Brem and Morton (1955) were originally diagnosed, on lymph-node sections, as follicular lymphoblastoma, although these diagnoses were later rescinded. It cannot be denied that this condition might be familial in origin, expressing itself later in life, as is the case, for example, in Huntington's chorea. This, however, seems unlikely when one considers the very nature of the malady and the clinical features of the other congenital conditions due to the absence of specific plasma-proteins, for example, afibrinogenaemia. Brem and Morton (1955) considered that the lymph-node changes in such patients might be the result of agammaglobulinaemia rather than the cause, but a similar pathological change was not demonstrated in the lymph-node of a patient with long-standing congenital agammaglobulinaemia (Young, Wolfson, and Cohn, 1955).

We consider that our first patient may be placed in this group, since he had no gamma globulin demonstrable by electrophoresis and his peripheral lymphocyte count was normal, though his lymph-nodes showed reactive hyperplasia. No plasma cells could be distinguished in his lymph-nodes, but a few were seen in the lamina propria of the small intestine, and were less numerous than normal. These findings, together with an onset of infective episodes at three and a half years of age, would be compatible with the classification of this case as

congenital agammaglobulinaemia. The study of the patient's ability to produce antibodies, however, revealed that he responded normally to *S. paratyphi B* but not to *S. typhi* (Table IV), and that his isohaemagglutinin titre was normal. These results, together with splenomegaly, justify the classification of his condition as primary acquired agammaglobulinaemia. Unfortunately neither his parents nor his sister were available for study.

Secondary acquired agammaglobulinaemia. By this name we refer to the electrophoretic absence of the gamma-globulin component which may be attributed to some known disease. This condition has been described in multiple myeloma (Snapper, Turner, and Moscovitz, 1953), lymphoma (Arends, Coonrad, and Rundles, 1954), and chronic lymphatic leukaemia (Brem and Morton, 1955; Warren and Kehoe, 1956; Jim and Reinhard, 1956). An absent serum-gamma-globulin peak in multiple myeloma was first noted by Snapper, Turner, and Moscovitz (1953); and Adams, Alling, and Lawrence (1949) emphasized the observation that a very low gamma-globulin peak is common in multiple myeloma, when the abnormal protein has not the same mobility as gamma globulin. They considered that this might be a constant and important feature of multiple myeloma. Young, Wolfson, and Cohn (1955) thought that this diminution or absence of gamma globulin in multiple myeloma might be due to the removal of gamma-globulin precursors, manufactured in the liver, by the abnormal plasma cells in their production of myeloma protein, leaving none for gamma-globulin synthesis. This hypothesis is not supported by the data concerning our patient with multiple myeloma (Case 2), because he had little urinary loss of protein and an almost normal serum-protein pattern, apart from the absence of gamma globulin. It seems just as likely that abnormal plasma cells may be unable to make normal gamma globulins, but that most patients with myelomatosis have sufficient normal or nearly normal plasma cells to synthesize enough antibodies for the prevention of recurrent infections, and for the maintenance of gamma globulin at a subnormal level.

Hypogammaglobulinaemia is a term coined to classify our fourth patient, whose serum had a normal electrophoretic pattern apart from a markedly diminished gamma-globulin level. It is thought that he may have an undescribed disorder in which leg ulcers, hypogammaglobulinaemia, splenomegaly, and neutropenia are associated, though the last named may be a 'secondary' phenomenon. The electrophoretic serum-protein patterns of his relatives are all normal.

Hypogammaglobulinaemia associated with hypoproteinaemia. By far the commonest of the conditions giving this protein picture is the nephrotic syndrome; but there remains an ill-defined group of patients with hypoproteinaemia in whom there is a lowered serum-albumin and serum-globulin level (Thompson, McQuarrie, and Bell, 1936; Rytand, 1942; Schick and Greenbaum, 1945; Krebs, 1946; Stern and Reiner, 1946; Hertzog and Faust, 1950; Wyngaarden, Crawford, Chamberlin, and Lever, 1952; Bound and Hackett, 1953; Fried and Henley, 1954), and in one instance (Bound and Hackett, 1953) no gamma globulin could be detected electrophoretically. These patients usually presented

generalized oedema and, more rarely, a history of infection (Wyngaarden, Crawford, Chamberlin, and Lever, 1952), and in the majority of cases no cause could be found. Our third patient, who had follicular lymphoblastoma, may be classified in this category. His clinical course was principally that of a severe hypoproteinaemia, with recurrent bouts of oedema, but no significant history of infections, although his gamma globulins were always markedly reduced (Plate 23, Fig. 7) and he had a severe leucopenia. He developed 'electrophoretic' agammaglobulinaemia only as a terminal event, when the effects of his disease and malnutrition also reduced his albumin level to that of the $alpha_1$ and $alpha_2$ components (Plate 23, Fig. 7*d*).

Hypogammaglobulinaemia associated with the familial dysproteinaemia of Homburger. This dysproteinaemia, first described by Homburger and Petermann (1949), is characterized by the familial occurrence of oedema of the legs, associated with leg ulcers in male and with functional vascular changes in female patients. Examination of the patients' sera revealed dysproteinaemia, which may be detected only by electrophoresis and may vary from relative to relative. The frequency of leg ulcers in the male members of this group is especially interesting in view of their presence in our patient with hypogammaglobulinaemia.

'Agammaglobulinaemia' and Immunity

Resistance and agammaglobulinaemia. The factors concerned in the congenital and acquired resistance of species and individuals to infection are slowly being defined. These factors may be passively present, for example, complement or properdin, or may have to be actively formed or stimulated, as in antibody formation, leucocyte response, phagocytosis, and the repair of diseased tissue. The importance of immunoglobulins in resistance to infections is emphasized by the recurrent pyogenic infections which occur in patients with agammaglobulinaemia, and which can often be eliminated by monthly injections of gamma globulins. Some reported patients, however, have shown no increased liability to infection, in spite of a persistently absent gamma-globulin peak on electrophoresis (Brem and Morton, 1955), whereas others have had recurrent infections in spite of a gamma-globulin level of 110 mg. per 100 ml. (Martin, Gordon, and McCullough, 1956), which would be considered an adequate therapeutic level in patients with congenital agammaglobulinaemia (Good and Mazzitello, 1956). Our patient with myeloma had the lowest level of gamma globulin, but was not troubled with infections; and furthermore, our third and fourth patients, with comparable degrees of hypogammaglobulinaemia and leucopenia, differed markedly in their liability to infective episodes. This finding supports the contention that there may be some factors other than agammaglobulinaemia causing the lowered resistance in such patients (Raffel, 1956); but studies of properdin levels, for example, in these patients have so far proved inconclusive (Wardlaw, Blum, and Pillemer, 1955; Pillemer, 1955; Skahen, Fien, and Kirsch, 1955).

Tables I and II show that a poor leucocyte response to infection occurred in a number of patients, the majority of whom responded to antibiotics and gamma-globulin therapy, but not to gamma globulin alone, while in this group there were also instances in which there was no response to therapy and the patients died of infection (Brem and Morton, 1955; Hutchison, 1955). The poor leucocyte response in some of the patients with primary acquired agammaglobulinaemia was attributable to hypersplenism, and was relieved by splenectomy. If there is an inadequate leucocyte response which cannot be remedied by splenectomy, it appears to be advisable to use both antibiotics and gamma globulins for the control of infective episodes and for prophylaxis.

Janeway, Apt, and Gitlin (1953) have emphasized the observation that patients with agammaglobulinaemia may readily be overwhelmed by bacterial infections, but that they respond normally to viral challenge, although they may be subject to several recurrences owing to the lack of antibody formation (Bruton, 1952).

Gamma globulins are a collection of many heterogeneous proteins, whose properties may differ widely. One component, for example, may combine with an antigen forming a precipitate, while another component may prevent such a combination (Zinneman, Hall, and Heller, 1954). This variation within the gamma globulins themselves may partly explain the variations in resistance encountered in agammaglobulinaemic patients. The adequate response of the body to bacterial invasion is to localize it, destroy it, and repair the damage. There may be difficulty in localization with congenital afibrinogenaemia (Prentice, 1951), and in localization and destruction of the organism in leucopenia and agammaglobulinaemia. The history of slow healing of wounds in our fourth patient, and his unusual 'tissue-paper' scars and leg ulcers, suggest that he may have some inherent defect in repair. This might be related to the permeability factor in wound healing, which is thought to be a gamma globulin (Cameron, 1956).

Allergic reactions. Although patients with agammaglobulinaemia cannot produce antibodies, they may be susceptible to hypersensitive reactions and some allergic phenomena. Our first patient died suddenly after an anti-cholera injection, and was found to have extensive haemorrhages into both suprarenals which may have represented a Schwartzmann type of reaction. Porter (1956) converted the reaction of a Mantoux-negative patient with congenital agammaglobulinaemia by giving B.C.G., and was able to transfer the induced tuberculin sensitivity to a Mantoux-negative normal subject by the injection of the patient's leucocytes. We do not yet know whether this result means that the small amounts of gamma globulin produced in a patient with agammaglobulinaemia are sufficient to make possible the development of hypersensitivity, or whether sensitization is not affected by the body's ability to produce gamma globulin.

Site of antibody formation. The exact origin of the immunoglobulins, and gamma globulins in general, is still debatable. There is an almost equal weight of experimental evidence favouring the lymphocyte and the plasma cell as the

source of these proteins, and it has been suggested that both these cells may be derived from a common stem cell, and may have an equally important part in the formation of the immunoglobulins (Harris and Harris, 1956). Patients with congenital agammaglobulinaemia have an almost complete absence both of plasma cells and of a response of their lymphoid tissue to antigenic stimulation when compared with normal subjects (Good, 1954). This observation furnishes further evidence that gamma globulin is produced by the plasma cell; but Young, Wolfson, and Cohn (1955) have also reported a marked reduction of lymphocytes in their patients, both in lymphatic tissue and in the peripheral blood, and in Keidan's atypical patient (Keidan, McCarthy, and Haworth, 1953) there was actually an abundance of plasma cells but an absence of lymphocytes in the lymphoid tissue. Our first patient had abundant germinal centres, but no identifiable plasma cells, in lymph-node sections, and a markedly reduced number in the lamina propria of the small intestine and in the bone-marrow; the third patient had a normal number of plasma cells in the lamina propria of the small intestine and in other tissues. The study of these patients, therefore, has so far yielded no conclusive evidence as to the precise tissue-cells which synthesize gamma globulins, but supports the importance of lymphocytes and plasma cells in this regard.

Transplantation of tissues. By the successful skin homoeo-graft to a patient with agammaglobulinaemia Good and Varco (1955) opened a new field of investigation in this condition. Previous attempts at homoeo-transplantation of viscera, such as a kidney, have so far failed because antibodies develop, although the kidney has remained viable for many months in some instances (Hume, Merrill, Miller, and Thorn, 1955); but Merrill, Murray, Harrison, and Guild (1956) have reported a successful renal transplantation from one identical twin to another. In a recent leading article in the *Lancet* (1956) it was suggested that if complete agammaglobulinaemia, or the total arrest of antibody formation, could be induced, such transplants would be successful, but 'it may exchange one fatal disease for another'. A study of the acquired forms of agammaglobulinaemia may lead to a safe method of beneficial induction, and a close investigation of the altered metabolism and results of treatment in all available patients could result in practical means of permanent induction of hypogammaglobulinaemia. Since it has been shown that such patients cannot manufacture antibodies, even when supplied with injected gamma globulins (Martin, Gordon, and McCullough, 1956), there would be no objections to monthly maintenance injections of gamma globulins. While the majority of patients reported (Tables I and II) have been adequately controlled by monthly injections of gamma globulins, a few, as we mentioned previously, have responded only to antibiotics, or have required both antibiotics and gamma globulin, and some have died despite all therapeutic measures (Keidan, McCarthy, and Haworth, 1953; Hayles, Stickler, and McKenzie, 1954; Hutchison, 1955). The reason for these varying responses to therapy is not obvious, but is of great practical importance.

Associated Phenomena

Diarrhoea and steatorrhoea. Diarrhoea has been a frequent finding in all types of agammaglobulinaemia, and has been ascribed to recurrent enteric infections, although in some instances stool cultures were negative (Hutchison, 1955). Two of our patients (Cases 1 and 3) had diarrhoea, and in both instances no pathogen was isolated from the stools. Autopsy in Case 1 showed marked lymphatic hypertrophy (Plate 20, Fig. 1). Unfortunately no estimations of fat were performed in the stools, but the other patient (Case 3) had demonstrable steatorrhoea, and excreted 9·8 g. of fat per day on a diet of 90 g. of fat per day. Steatorrhoea was reported in the one female patient with congenital agammaglobulinaemia (Sanford, Favour, and Tribeman, 1954), in three patients with primary acquired agammaglobulinaemia (Rohn, Behnke, and Bond, 1955; Rosecan, Trobaugh, and Danforth, 1955), and in one patient with secondary acquired agammaglobulinaemia due to a malignant lymphoma (Arends, Coonrad, and Rundles, 1954). Our patient with steatorrhoea resembled the last-mentioned patient in that he had a reticulosis, but at autopsy there was no involvement of the bowel.

Haematological aspects of agammaglobulinaemia. The lymphopenia associated with congenital agammaglobulinaemia has already been mentioned. Frick and Good (1956) studied seven patients with agammaglobulinaemia, and noted that a high platelet count occurred in all four cases of the congenital variety, and in one other. Coagulation studies carried out in these patients gave normal results, indicating that gamma globulins play no significant part in normal blood coagulation. Good and Kelley (1955) reported the complete absence of eosinophils in one patient, but in four other patients found a normal count, which reacted appropriately to the intramuscular injection of corticotrophin. A leucopenia, or a poor leucocyte response to infection associated with splenomegaly, has been reported on several occasions in primary acquired agammaglobulinaemia, and occurred in three of our patients. Splenectomy has been reported to have cured two patients with pancytopenia (Prasad and Koza, 1954; Rohn, Behnke, and Bond, 1955), and to have restored to normal the leucocyte count and its response to infection in another (Zinneman, Hall, and Heller, 1954). This result is evidence of hypersplenism, which may also be a factor in the poor leucocyte responses in other patients with splenomegaly (Table II).

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Summary

Four patients with low gamma-globulin levels are reported, with the results of electrophoretic and immunological studies.

The features of cases of 'agammaglobulinaemia' are discussed, with special reference to their classification and to their importance in problems of resistance and immunity.

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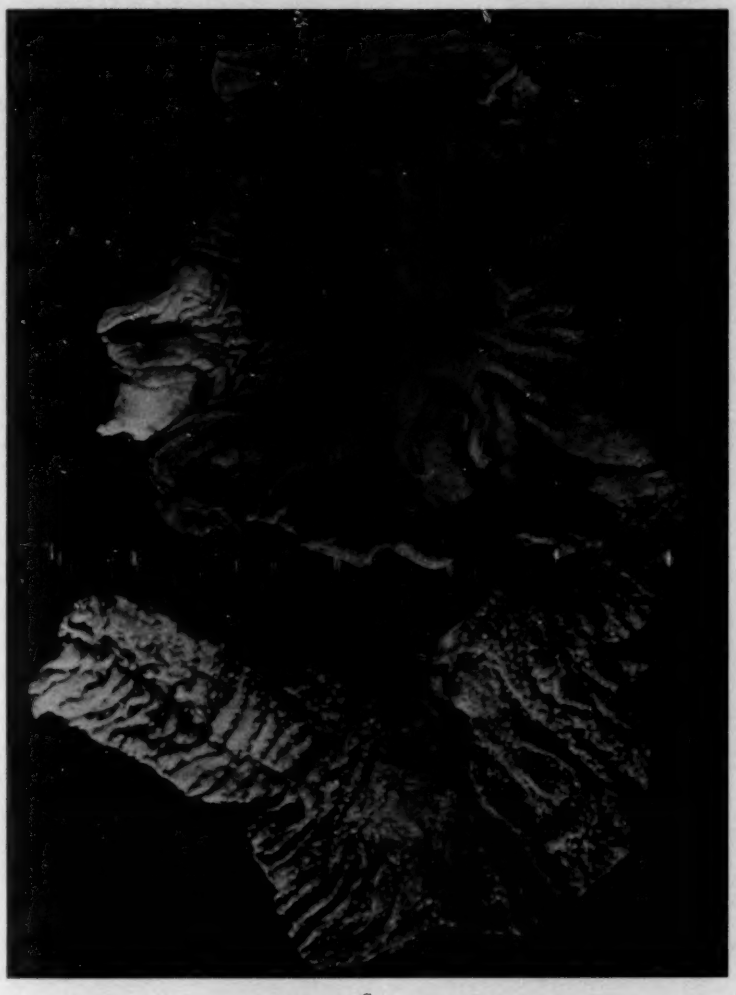
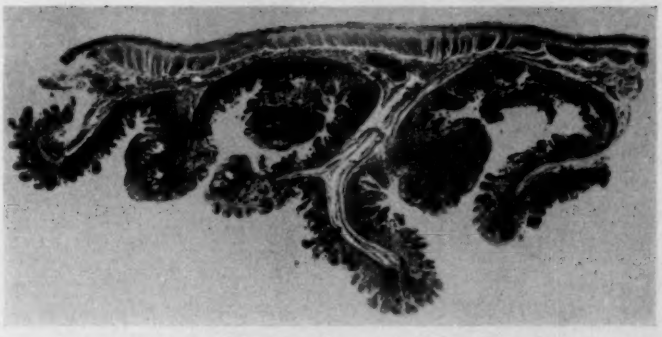


a



b

FIG. 1. (*a*) Portion of stomach and duodenum, showing numerous small polyps due to lymphoid hyperplasia in the duodenum
(*b*) Duodenal polyp showing lymphoid hyperplasia (× 10) (Case 1)

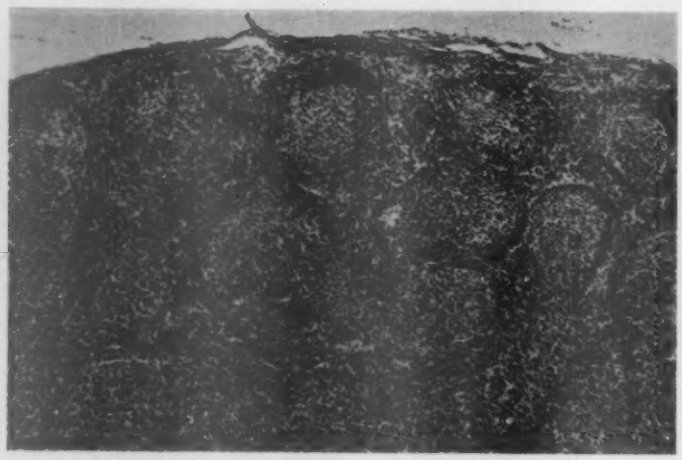


FIG. 2. Lymph-node biopsy. There is less demarcation between the follicles and the rest of the node than previously (Case 3)

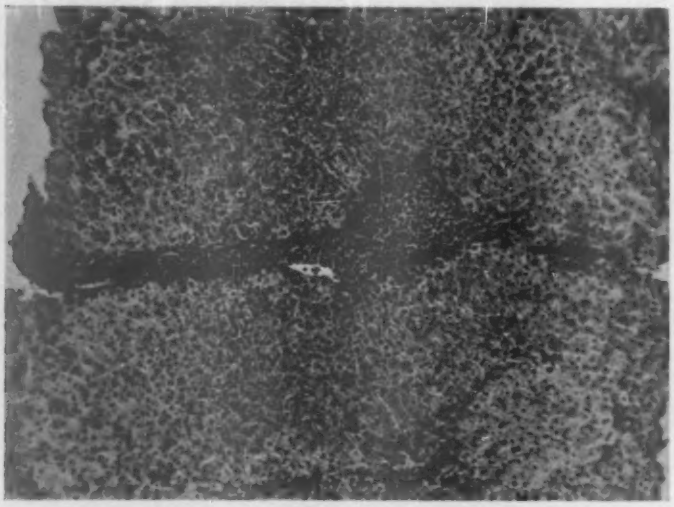


FIG. 3. Liver biopsy. Intense infiltration of the portal tracts with lymphocytes (Case 3)

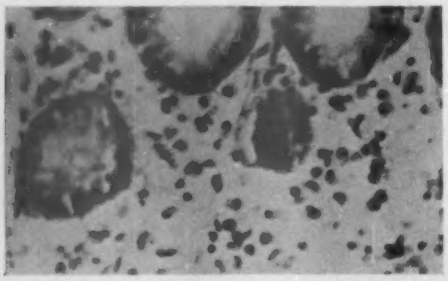


FIG. 4. A group of plasma cells in the lamina propria of the small intestine (Case 3)

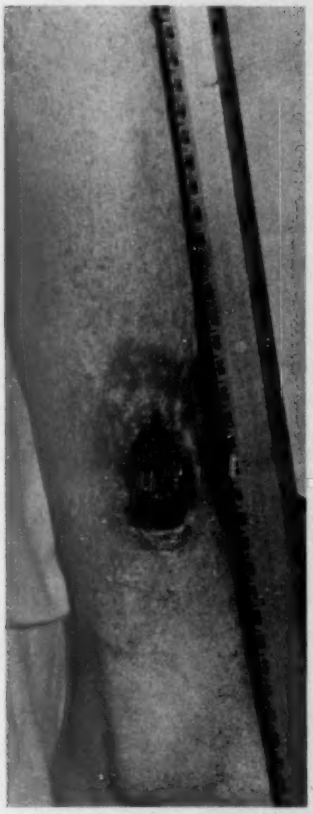


FIG. 5. Ulcer on the lateral aspect of the right leg (Case 4)

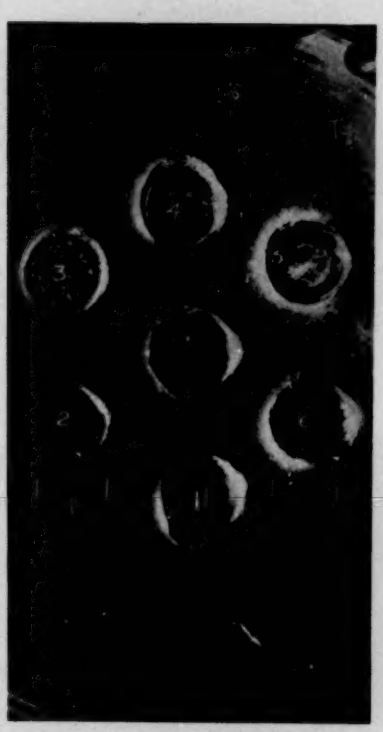
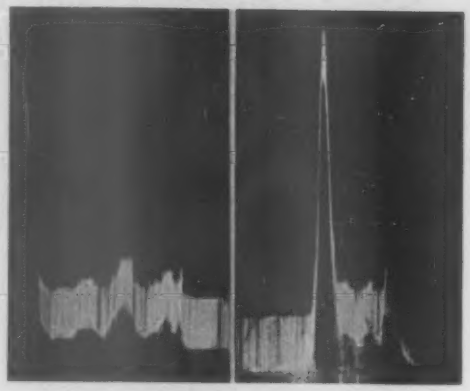


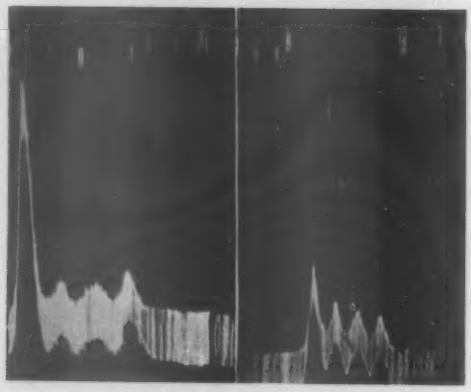
FIG. 6. The central cup contains undiluted anti-gamma-globulin serum. Cup 1 contains normal serum diluted 1/100. Cup 2 contains undiluted serum of patient No. 1. Cup 3 contains undiluted serum of patient No. 3. Cup 4 contains undiluted serum of patient No. 2. Cup 5 contains undiluted serum of a patient with congenital agammaglobulinaemia, and cup 6 contains undiluted serum of patient No. 4. The serum from patient No. 2 appeared to contain the least gamma globulin, since the precipitate between cup 4 and the central cup was the last to develop and was the weakest. On the other hand, the serum from patient No. 4 appeared to contain the most gamma globulin, since the precipitate was the first to develop and was the most prominent



a *b*

(*a*) Normal

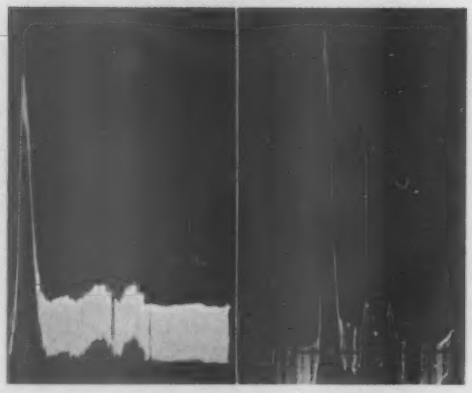
(*b*) Case 2. Absent gamma-globulin fraction



c *d*

(*c*) Case 3. All fractions are diminished, and virtually no gamma-globulin fraction can be seen. This pattern was typical of many found at earlier stages in the patient's illness

(*d*) Case 3 late in the course of the illness. Markedly reduced albumin level and no gamma globulin



e *f*

(*e*) Case 4. No gamma globulin, but otherwise normal pattern

(*f*) A case of congenitala gammaglobulinaemia. Complete absence of gamma globulin. The peak at the extreme right is due to a boundary anomaly

FIG. 7. Moving-boundary electrophoretic patterns of serum-proteins

616-003.821:616.8

PRIMARY AMYLOIDOSIS[1]

With Special Reference to Involvement of the Nervous System

By R. A. CHAMBERS, W. E. MEDD, and H. SPENCER

(From St. Thomas's Hospital and the National Hospital for Nervous Diseases, London)

With Plates 24 to 26

The simplest classification of amyloidosis divides it into primary and secondary forms, on the grounds of the absence of any associated disease and the less constant staining reactions in primary amyloidosis, and the tendency of the deposits to occur in different sites in the two forms. The rigidity of this distinction is being increasingly questioned as more cases with mixed features are reported (for example, Symmers, 1956*a*, and Case 3 of the present paper). Primary amyloidosis has itself been divided into those cases in which there is one localized tumour and those in which the deposits are more generalized. The present paper describes six generalized cases, three of which initially presented neurological problems, and an attempt is made to define the characteristic features of the illness.

Case Reports

Case 1 (STH A. 84627). A housewife aged 54 was admitted to hospital on 22.12.54 complaining of a painless swelling under the jaw for seven months, of shortness of breath for four months, and of swollen ankles for one month. She could only walk slowly because of dyspnoea, and she had had two recent attacks of paroxysmal nocturnal dyspnoea. The family history was negative except that her mother had died at 70 years of an illness 'involving the heart and liver'.

Her speech was slightly slurred: her tongue was enlarged, and she was unable to protrude it completely. There was a diffuse, firm, painless, immobile swelling under the jaw on both sides (Plate 24, Fig. 2). At post-mortem examination these were found to be due to enlargement of the base of the tongue (Plate 24, Fig. 3). There was considerable firm, smooth enlargement of the liver and spleen. The pulse-rate was 100 to 110 and regular apart from ectopic beats, the blood-pressure was 120/70, and the venous pressure was raised 5 cm. above the sternal angle. The apex beat was normal, and there was a soft systolic murmur at the apex, but no added sounds or diastolic murmurs. There were crepitations at the lung bases, and the ankles were oedematous. Because of the normal blood-pressure and absence of valvular disease a myocardial cause for the cardiac failure was assumed, and in view of the enlargement of the tongue, liver, and spleen, primary amyloidosis was diagnosed.

[1] Received June 29, 1957.

Investigations. The urine contained 3·5 g. of protein per litre (Esbach). When this protein had been precipitated by heat and filtered, the filtrate contained a protein which could be precipitated with 25 per cent. salicylsulphonic acid and was shown by electrophoresis to lie between the α_2 and β globulin bands. A similar band was found on serum electrophoresis. The erythrocyte sedimentation rate (Westergren) was 33 mm. in one hour. The serum-proteins were 4·9 g.

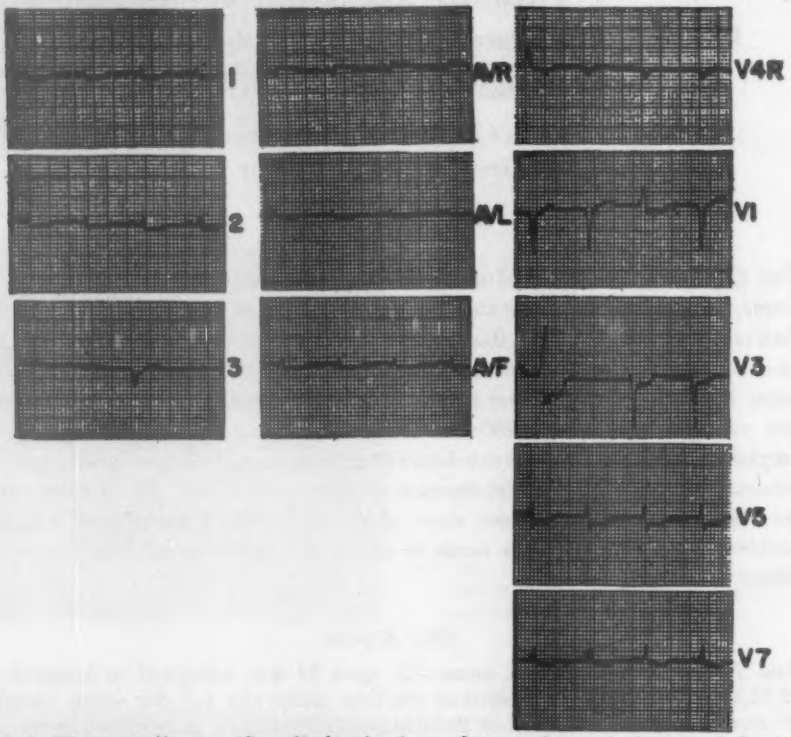


FIG. 1. Electrocardiogram (Case 1) showing low voltage and ventricular ectopic beats.

per 100 ml. (albumin 3·5 g., globulin 1·4 g.). A Congo-red test showed 78 per cent. clearance of the dye at half an hour, but no increased clearance in the next half hour, and none appeared in the urine during the first hour after its injection. This result was considered equivocal. Chest X-rays showed bilateral pleural effusions, but the transverse diameter of the heart was not increased. An electrocardiogram (Fig. 1) showed low-voltage complexes, multiple ventricular ectopic beats, and inversion of the T waves and lowered S-T segments in left ventricular surface leads. The T-wave and S-T abnormalities were considered to be, at least partly, due to digitalis. An aspiration liver biopsy showed inconspicuous amyloid deposition around the basement-membrane of the liver sinusoids. This was unnoticed in the biopsy sections, and was only recognized in the post-mortem sections (Plate 24, Fig. 4). Treatment with rest, digitalis and mersalyl was continued without significant improvement, and on 4.1.55 the patient died suddenly of left ventricular failure.

Post-mortem findings. The heart weighed 420 g., and the anterior wall of the left ventricle dimpled slightly. The cavities were not enlarged, and the endocardial surface showed a purple and yellow mottling. Iodine stained the heart

muscle chestnut brown, particularly the subendocardial tissue. The lungs showed partial collapse of both lower lobes owing to bilateral pleural effusions. The tongue measured 9 cm. anteroposteriorly, and 4·2 cm. in thickness at the foramen caecum (Plate 24, Fig. 3). The enlargement was due to increased bulk of the intrinsic muscles, excluding the genio-hyoglossi, which were normal. The gastrointestinal tract was normal. The liver was enlarged, and weighed 1,930 g., and the cut surface was waxy and bloodless. The spleen weighed 220 g., and was hard and diffusely infiltrated with amyloid, which had been stained by the Congo red injected *in vivo*. The Malpighian corpuscles could not be identified. The kidneys weighed 140 g. and 130 g.; they were small, with thinned cortices, and no amyloid could be demonstrated. The pancreas was firm and waxy. Several bones were examined, and myelomatosis was excluded. The tongue, liver, and pancreas all gave a strongly positive iodine test.

Microscopic examination showed diffuse interstitial amyloid infiltration round vessels and beneath the pericardium of the left ventricle. There were many small subendocardial infarcts, both recent and healing, which, in the absence of coronary atheroma, were attributed to the amyloid change. In the lung there were periarterial and diffuse alveolar deposits of amyloid related to alveolar capillary basement-membranes. The stomach showed diffuse amyloid infiltration of the lamina propria. Both the liver and the spleen were diffusely infiltrated with amyloid, and in the pancreas this infiltration had caused partial atrophy of exocrine tissue. Amyloid was present in the periadrenal capsules, but the glands themselves were normal. The kidney contained no amyloid, but the appearances were similar to those seen in multiple myelomatosis. Many of the glomeruli and tubules were extensively damaged; the latter were blocked by colloid casts, and in places the epithelium of the convoluted tubules was loaded with hyaline droplets. Voluntary muscle from the tongue (Plate 24, Fig. 5) and from the pectoralis major contained abundant amyloid material, both in the interstitial tissues and within the fibres, many of which were greatly swollen and had lost their normal striation. There was no proliferation of sarcolemmal nuclei or atrophy of fibres to suggest damage to peripheral nerves.

Case 2 (STH A. 33735). A housewife aged 57 was admitted to hospital on 10.11.52. Six years previously she had given up playing the clarinet because her fingers had become enlarged and her tongue and face had become thickened. For three years she had noticed dyspnoea, which had become worse, and had been accompanied by oedema in the last three months. Her speech had become indistinct.

Her features were coarse, the lips thickened, and the tongue much enlarged (Plate 25, Fig. 6). Her fingers were thickened and covered with purplish subcutaneous nodules 3 to 6 mm. in diameter (Plate 25, Fig. 7), and there were petechiae on her face, neck, tongue, and hands. The pulse was regular, the blood-pressure was 180–130, the venous pressure was raised 7·5 cm. above the sternal angle, and there was oedema of the legs and sacrum. There were bilateral pleural effusions, and crepitations at both lung bases.

Investigations. The urine contained 4 to 10 g. of protein per litre (Esbach). The erythrocyte sedimentation rate (Westergren) was 17 mm. in one hour. The serum-proteins were 5·4 g. per 100 ml. (albumin 3·1 g., globulin 2·3 g.). The blood-urea level was normal. Chest X-rays showed enlargement of the heart, mainly due to the left ventricle, and bilateral pleural effusions. An electrocardiogram showed low-voltage complexes and ventricular ectopic beats. A skin biopsy (Dr. I. Whimster) showed replacement of most of the collagen in the dermis by coarse clumps of fibrillary material, with intervening clefts, some of

which appeared to be artifacts; others had a lining of flattened nuclei. The abnormal substance appeared to be altered collagen, and did not give the staining reactions of normal collagen, collagen altered by solar exposure, or amyloid. A small conjunctival nodule gave a similar histological picture. Biopsy from a finger, two days after an intradermal injection of Congo red, showed that the abnormal material in the dermis had selectively retained the dye.

The patient was treated with digitalis and mersalyl, and temporarily improved, but had to be readmitted twice in 1953. She was later twice admitted to the Bristol Royal Infirmary because of exacerbations of cardiac failure, and she died suddenly on 15.2.54.

Post-mortem findings. The pericardial sac had a greyish granular appearance, and the heart was greatly enlarged, weighing 590 g. Both ventricles were thickened; the myocardium was pale, and contained a few patches of fibrosis. The endocardium was also granular, and the inner surface of the left auricle was opalescent. Both lungs showed pressure collapse. The tongue was enlarged, measuring 9·5 cm. from the tip to the vallecular fossa and 7·0 cm. in width. The intestinal tract was normal apart from roughening of the serosa and an acute duodenal ulcer 0·4 cm. in diameter. The liver weighed 1,230 g., and showed no amyloid. The left kidney weighed 190 g. and the right 185 g., and both were swollen and pale, with lipoid flecks in the cortex. The spleen and the endocrine glands were normal. The inner surface of the dura in the cervical region was granular. The iodine test for amyloid was uniformly negative.

Microscopic examination showed extensive amyloid deposits in the endocardium and pericardium. There was diffuse interstitial infiltration of the myocardium. Apart from slight amyloid infiltration in the adventitia, the branches of the coronary arteries were normal, although the coronary veins showed extensive medial infiltration. Some myocardial fibres were atrophied, and there were areas of fibrotic replacement. There were amyloid deposits in the adventitia and walls of the vasa vasorum of the aorta. The lungs showed amyloid infiltration of the walls of the pulmonary veins, but the alveoli were unaffected. There were amyloid deposits in the branches of the hepatic artery and portal vein within the liver, but the hepatic veins were unaffected, and there was no parenchymal infiltration. There was widespread infiltration of the interstitial tissues of the tongue, causing muscular atrophy, and extensive infiltration of the interstitial tissues in the walls of the oesophagus, stomach, and small intestine. In the stomach and small intestine the lamina propria was the principal site of deposition, and the muscularis mucosae was severely damaged. The degree of amyloid infiltration decreased towards the lower small intestine. The kidneys showed amyloid changes in the walls of the arteries, arterioles, and veins, and in many glomeruli. The tubular basement-membranes were unaffected. The blood-vessels in the adrenals and pancreas were involved. There were deposits of amyloid in the spinal dura mater, but no deposits were found within the central nervous system. Both sciatic and femoral nerves showed amyloid infiltration of the intraneural blood-vessels and patchy infiltration of the perineurium, but there was no demyelination or axonal degeneration. Methyl violet and Congo red both stained the amyloid throughout, but iodine failed to do so.

Case 3 (STH A. 77020). A spinster of 52 was admitted to hospital on 2.9.54, complaining of increasing lethargy and anorexia for 10 months. For two years there had been oedema of the ankles, and she had been short of breath. Recently she had passed urine thrice nightly, but she had no dysuria. For two weeks before admission she had had pain in the right hypochondrium and vomiting.

Her complexion was sallow, and the skin, particularly in the creases, was pig-

mented, but there was no buccal pigmentation. The blood-pressure was 130/85, and there was no abnormality of the heart. There was slight oedema of the ankles. The nervous system was normal. The specific gravity of the urine was 1,016 to 1,020; it contained much protein, and an occasional leucocyte and red blood cell, and was sterile. Renal failure was diagnosed.

Investigations. The erythrocyte sedimentation rate (Westergren) was 117 mm. in one hour. The serum-proteins were 5·6 g. per 100 ml. (albumin 2·9 g., globulin 2·7 g.). The blood-urea was 38 mg. per 100 ml. A urea clearance test showed 44 per cent. of average normal function, and the urea concentration test gave a maximum concentration of 2·2 per cent. An intravenous pyelogram was normal.

In spite of the pigmentation and weakness, Addison's disease was thought unlikely, since a 24-hour specimen of urine showed a ketosteroid content of 5·1 mg. and the first part of the Kepler test was negative. Amyloid disease was suggested because of the association of severe proteinuria and pigmentation. A Congo-red test confirmed this diagnosis: 30 minutes after intravenous injection of 10 ml. of a 1 per cent. solution none was detectable in the blood and none appeared in the urine. In view of this diagnosis it was thought necessary to exclude the presence of intra-abdominal suppuration. At laparotomy on 15.10.54 the only abnormal finding was a slightly thickened gall-bladder, which was removed. After the operation there was persistent hypotension, with suppression of urine, until death occurred from uraemia two days later.

Post-mortem findings. The pericardium and heart were normal. The lungs were extensively collapsed and airless, and felt indurated and rubbery, especially at the apices. There was no pulmonary infection. The intestinal tract was normal. The liver was a little enlarged, was pale, and had been stained by the Congo red injected *in vivo*. The spleen was of normal size, and was diffusely filled with glairy material stained by Congo red. The kidneys weighed 250 and 170 g., and were large and pale, with a thickened, pale-yellow cortex and normal reddish medulla. There was ante-mortem thrombus in the branches of the right renal veins. The cortex of both adrenal glands contained amyloid stained with Congo red. The pancreas was replaced by translucent reddish tissue, and had almost lost its lobular pattern. The remainder of the endocrine system, and the nervous and the skeletal systems, were normal. None of the organs gave a positive result with the iodine test for amyloid.

Microscopic examination showed extensive amyloid infiltration of the renal glomeruli, the tubular basement-membranes, and the medullary stroma, which had led to severe tubular damage. The epithelium of the convoluted tubules was loaded with hyaline droplets, and the cells of the proximal tubules contained abundant fat. There was diffuse amyloid infiltration of the spleen, adrenal cortex, and liver, and of the pancreas, in which the exocrine tissue was almost completely destroyed, though some of the islet tissue survived. There was diffuse amyloid infiltration of the lungs, and the change appeared to have started in the basement-membrane of the alveolar capillaries, which in many places were compressed and obstructed by the extensive deposits. There was also some collapse and patchy bronchopneumonia. There was amyloid infiltration of an anthracotic hilar lymph-gland. The heart muscle was normal. Amyloid deposits were present in the endoneurium of the autonomic nerves in and about the pancreas. The amyloid material did not give the usual staining reactions with methyl violet, though it selectively absorbed Congo red.

Case 4 (NHQS 55065). A pensioner aged 42 was admitted to hospital in November 1945, complaining of weakness of the legs for 12 years and of the hands and

arms for nine years. He had always been healthy, and came of a healthy family. When he was 30 years old his right knee became swollen, painful, and red for a few days. As this attack subsided, he developed stabbing pains in the left, then in the right calf and shin, and these pains persisted. His left foot became painful to walk on, and an infected callosity developed under the ball of the foot. A year later he noticed numbness below the knees, which slowly extended upwards, and in the following year he became unable to dorsiflex the ankle. Both legs became slowly weaker, and he required a stick for walking. He then noticed paraesthesiae in the fingers of both hands; the paraesthesiae slowly extended to just above the elbows, and the fingers, wrists, and elbows were also weak. Throughout these events he felt ill, and exhausted by any effort, and had grown slightly deaf in his left ear.

He walked on a wide base, with a high-stepping gait, and Romberg's sign was positive. The pupils reacted better to convergence than to light. There was perceptive deafness on the left, and his tongue was wasted and fasciculating. There was symmetrical wasting and weakness of the upper limbs, most marked distally, and a bilateral claw-hand deformity. Both arms were hypotonic, and fasciculations were seen in all their muscles. Opposition and abduction of the thumbs were reduced, and finger movements were clumsy. There was wasting of the leg muscles, worse distally, and bilateral foot-drop. The left foot was shortened and broadened (Plate 25, Fig. 8), and a perforating ulcer was present on the sole. Both legs were hypotonic, and there was slight weakness at the hips, moderate weakness at the knees, and severe weakness at the ankles and toes. There was a mild sensory ataxia. The tendon-reflexes, lower abdominal reflexes, and plantar responses were absent. Pin-prick and temperature appreciation was absent below the knees, and impaired below the middle of the thighs and upper arms. Light touch was not felt over the feet, and was impaired below the knees and elbows. Vibration sense was impaired at the wrist and ankles, and joint-position sense was impaired in the toes and fingers. Deep-pain sensitivity was impaired in the Achilles tendons. The great auricular and supraclavicular nerves, and the musculocutaneous nerves of the legs, were pathologically enlarged. General examination showed him to be a thin, ill man, but no other abnormalities were found.

Investigations. The erythrocyte sedimentation rate (Wintrobe) was 25 mm. in one hour. There was no albuminuria, and serum electrophoresis was normal. The Wassermann reaction was negative in the blood and cerebrospinal fluid. The cerebrospinal fluid was twice found to be normal, but contained 50 mg. of protein per 100 ml. on one occasion. X-rays of the left foot showed advanced destruction of bone, with almost complete disappearance of the metatarsals and proximal phalanges. The electromyogram showed incomplete lower-motor-neurone disease, with a relative absence of denervation activity. The triple response was absent on all parts of the skin, whether sought by scratching or by pricking with histamine. A biopsy of the left great auricular and an interdigital nerve showed relatively large amounts of connective tissue round the nerve-bundles. The perineurium and endoneurium, and the walls of some vessels in both nerves, contained amyloid; these changes were more advanced in the interdigital nerve. *M. leprae* were not seen.

On 26.12.56 the patient suddenly lost consciousness for half an hour, and the next day complained of pain in the chest; he became shocked, was found to have auricular fibrillation, and was in cardiac failure. He was admitted to hospital, and made a gradual recovery, punctuated by brief attacks of unconsciousness. Thus, after 14 years, the first clinical evidence of involvement of tissues other than the nervous system appeared.

Case 5 (NHQS 46987). A waiter aged 35 was admitted to hospital on 13.7.55 complaining of diarrhoea, impotence, and weakness of the legs. He was a Cypriot, and came of a healthy family. When aged 31 he had complained of malaise, occasional vomiting, and inability to shout. He then developed constipation, and attacks of burning rectal pain associated with a desire to defaecate. These attacks, lasting 10 minutes, occurred three or four times a day, and led to rectal prolapse. Two months later painless diarrhoea supervened, and the rectal pains disappeared. There was mucus, but no blood, in the stools, which he passed 10 or more times daily. (The patient had lost weight continuously since diarrhoea began.) Later, stabbing pains developed in his toes, occurring at intervals of five to ten minutes and causing his legs to jump, and similar pains occurred in his penis. The blankets on his bed felt heavy, and he had transient burning sensations of his feet and legs. Six months later he awoke with large, painless blisters on his legs, due to hot-water-bottle burns, and it was found that his legs were anaesthetic. The burns healed satisfactorily, and the anaesthesia was considered hysterical. Since then the lower two-thirds of his thighs had become numb. He noticed that a chronic rash on his feet no longer itched, and his hands and feet had ceased to sweat. During the next two months he became impotent. About two years after the onset of his illness he noticed weakness of his ankles, worse on the right; this weakness later involved the rest of his legs, and he could only walk 50 yards. Malaise, lack of energy, and occasional vomiting persisted. He had noticed flickering of the muscles of his arms, legs, and trunk. At one hospital, after a myelogram, he developed signs of meningeal irritation and retention of urine, but there was no other sphincter disturbance.

He occasionally shuffled as he walked; he turned unsteadily, and Romberg's sign was positive. There was no wasting of his arms, but the thenar muscles were pultaceous. There was hyperextensibility of the wrist and fingers, and the finger extensors were weak. All his leg muscles were small and hypotonic, and all the movements weak, the weakness increasing in severity from hips to ankles. Both ankle-jerks were absent, but the other tendon-reflexes and the abdominal reflexes were present. The plantar responses were absent. There was generalized insensitivity to pin-prick, complete over the feet, and partial over the front of the trunk, the forearms, hands, and legs; the upper quarter of the thighs was spared. Pain sense was reduced in the Achilles tendons. Heat (42° C) was appreciated only above the clavicles and in a vertical band down the spine. Cold (10° C) was appreciated over the upper half of the upper arms, the shoulders, most of the back, and the groins. Light touch sense was impaired over the hands, the lower two-thirds of the forearms, and the lower third of the thighs, and was absent below the knees. Joint-position sense was impaired in the toes, and vibration sense was impaired below the knees and wrists. Two-point discrimination was impaired over the finger-tips and soles of the feet. The external genitalia were anaesthetic. The great auricular nerves and the lateral popliteal and musculocutaneous nerves of the legs (Plate 25, Fig. 9) were abnormally thick. The skin was dry except over the face and in the axillae. There were scars of burns on his shins and calves, and abrasions and ulcers on his feet. The triple response was everywhere absent: wealing and the local red reaction were present, but the flare was absent after pricking with histamine, in all parts of the limbs, trunk, neck, cheeks, and forehead. Flushing was produced by inhalation of amyl nitrite. The patient's oral temperature was raised by a heat cradle to 100·5° F, and sweating was absent below the elbows and groins, and over the front and sides of the trunk. He looked thin and tired, but no other abnormality was found on general examination.

Investigations. The erythrocyte sedimentation rate was normal. The urine

contained a trace of protein, pus cells, and *Bact. coli*. The Wassermann reaction was negative in the cerebrospinal fluid and blood. The cerebrospinal fluid was normal apart from a protein-content of 120 mg. per 100 ml. The serum-proteins were 6·24 g. per 100 ml. (albumin 3·15 g., globulin 3·09 g.), and electrophoresis was normal. The blood-urea and urea clearance were normal. The stools were fluid, but normal in composition apart from undigested meat-fibres. A fat-balance test, X-rays of the chest and feet, barium meal and follow-through, barium enema, sigmoidoscopy, and electrocardiogram were normal. Biopsies were taken of a peroneal muscle, the musculocutaneous nerve of the leg, and the overlying skin. The muscle showed occasional large swollen fibres, some containing amyloid material. The majority of the fibres were atrophic, but showed proliferation of sarcolemmal nuclei. The cross-striations in many of these atrophied fibres were still apparent. Among the bundles of nerve-fibres were clumps of amorphous, Congo-red positive, doubly refractile material, lying within the perineurium and between the nerve-bundles (Plate 26, Fig. 12). In some places there was loss of nerve-fibres. Small amounts of Congo-red positive material were present in some of the arrector pili muscles. *M. leprae* were not seen.

Case 6 (STH 224953). An electrician aged 33 was admitted to hospital on 21.2.49, complaining of numbness of the feet and weakness of the legs for two years, and of blurred vision in the left eye for one year. He had no relevant past or family history. At the age of 30 he noticed that he was unable to tell hot from cold on his feet, and that his legs tired quickly. A year later he became impotent, and began to have attacks of watery diarrhoea. Impairment of cutaneous sensibility below the knees was noted at another hospital, to which he was admitted with an appendix abscess. Two years later he began to have bouts of shooting pain in both calves, and noticed blurred vision in the left eye. He had felt tired throughout these occurrences, and had lost 35 lb. in weight.

He walked with a high-stepping, ataxic gait. His visual acuity on the right was 6/18, and on the left 6/24. The left fundus was obscured by vitreous opacities causing an irregular central scotoma. The pupils were of moderate size and irregular, and reacted well on convergence. The light reflex was sluggish in the right and absent in the left eye. There was slight wasting of the small muscles of the hands, and slight weakness of their grip. There was wasting of the muscles of the thighs, greatest in the adductors, and of all the muscles below the knees. There was hypotonia at the knees and ankles, and weakness at the knees, ankles, and toes, greatest in dorsiflexion and eversion. There was a mild sensory ataxia of the legs. The knee- and ankle-jerks were absent; the other tendon-reflexes, and the abdominal reflexes, were present and equal. The plantar responses were flexor. There was severe impairment of cutaneous pain sense below the middle of the thighs, and slight reduction over the fingers and hands. Appreciation of hot and cold was impaired over the same area. Light touch was dulled, and vibration sense reduced, below the knees, and joint-position sense was impaired in the toes. Deep-pain sense was reduced in the Achilles tendons. The skin of the hands, feet, and lower legs was dry, scaly, and pigmented, and there was a large healing ulcer over the left shin. Apart from arachnodactyly, physical examination was otherwise normal.

Investigations. The erythrocyte sedimentation rate was normal. The cerebrospinal fluid was examined twice, and was normal except for a protein-content of 70 mg. per 100 ml. on one occasion. The urine was normal, and the blood Wassermann reaction negative. An electromyogram showed decreased volitional activity in the quadriceps femoris and tibialis anterior muscles, and in the

first dorsal interosseus muscle of the left foot. Fibrillation was present at rest in the last two muscles, and they showed partial denervation. Biopsy of an interdigital nerve from the left foot showed the appearances of amyloid neuropathy, and amyloid deposits were present in a biopsy specimen from the subepidermal tissues of the gum.

A year later the patient showed wasting of the forearms, and his legs were thinner and weaker. The supinator reflexes, knee- and ankle-jerks, and plantar responses were absent. There were ulcers over both shins and an unnoticed burn on his left knee, and the lateral popliteal nerves were thickened. A Congo-red test gave a normal result. A few months later he had increasing weakness of the legs, difficulty in manipulating buttons, and alternating diarrhoea and constipation. Romberg's sign was positive, and there were early vitreous opacities in the right eye. Joint-position sense was defective in the fingers; the cutaneous sensory disturbance extended to the middle of his upper arms, and involved the whole of his legs, spreading to the buttocks. Appreciation of pin-prick and of hot and cold was more extensively affected than appreciation of light touch.

Two years later the patient was unable to walk without support, and had ulcerated buttocks. He was able only to count fingers with the right eye and detect hand movements with the left, and both fundi were obscured by vitreous opacities. There was normal power at the shoulders, and moderate or severe weakness at all other joints. The trunk muscles were weak, and the triceps jerks and abdominal reflexes were absent. The cutaneous sensory disturbance involved the shoulders, buttocks, and lower part of the abdomen, and vibration sense was impaired below the iliac crests and below the wrists. The blood-urea was 37 mg. per 100 ml., and the urea clearance test showed 70 per cent. of average normal function. The plasma-proteins were 5·8 g. per 100 ml. (albumin 3·5 g., globulin and fibrinogen 2·3 g.). An electrocardiogram was normal. During this period in hospital he had sudden episodes of unconsciousness lasting up to 10 minutes. An electroencephalogram was normal at rest, but on overbreathing gross instability ensued and the record was dominated by high-voltage activity at six cycles per second. This result was considered to be compatible with hypoglycaemia.

A year later his pupils had become fixed to light and convergence. His urine contained protein, but the blood-urea was normal, and the urea clearance still 70 per cent. Two months later he was readmitted, complaining of pain in the neck, shoulders, and abdomen, and of loss of urethal sensation. He was delirious, and disorientated in space, saying he was upside down. Muscular weakness had increased, and the sensory disturbance had extended to his trunk. The urine was heavily infected, and the blood urea was 123 mg. per 100 ml. An electrocardiogram showed flattening or inversion of the T waves in leads I, AVL, V5, and V7. Professor N. Martin found an abnormal globulin, in the region of β-globulin, in both serum and urine. The patient died of renal failure on 23.6.53.

Post-mortem findings. The heart weighed 490 g., and the left ventricle was hypertrophied. The myocardium was reddish-brown and firm. The aorta and its major branches were hypoplastic, and tore readily. The digestive tract was normal; the liver weighed 1,330 g., was pale, and showed no evidence of amyloid infiltration. The spleen was twice its normal size, and weighed 200 g. The cut surface was dark red, and did not appear to contain amyloid. Both kidneys were enlarged, weighing 191 g. and 198 g. respectively; the capsules stripped readily, exposing many small subcapsular abscesses. The cut surfaces also showed many abscesses, and papillitis necroticans had destroyed the medullae and renal papillae on both sides. The renal pelves and the bladder contained

pus. The adrenal cortices looked waxy, and the pancreas, though retaining a semblance of its lobular pattern, presented a glairy, translucent appearance on the cut surface. The thyroid was diffusely enlarged and pale, and contained a very small amount of colloid. The central and peripheral nervous systems showed no abnormality beyond slight thickening of the larger nerves such as the limb plexuses. There was considerable wasting and atrophy of the right first intercostal muscle. The iodine test for amyloid was negative except for a doubtfully positive reaction in the pancreas.

Microscopic appearances. There was acute pyelonephritis, and amyloid deposits were seen in the glomeruli and on the basement-membranes of the renal tubules, and had caused secondary ischaemic changes. There was diffuse amyloid infiltration throughout the pulp, and in some of the Malpighian corpuscles, of the spleen. There were deposits of amyloid material beneath the endocardium of the left ventricle. Deposits of amyloid were present on the cell-membranes of the periadrenal fat cells, in the endoneurial tissue of the periadrenal nerves, and beneath the capillaries of the adrenal cortex; they were also present in the interacinar tissue of the thyroid, causing acinar atrophy. In the pancreas the amyloid deposits had caused almost complete atrophy of the exocrine tissue, but atrophic islet tissue was present. Extensive perivascular deposits of amyloid were present in the pars anterior and pars posterior of the pituitary. In the liver amyloid had been deposited only on the basement-membranes of the small bile-ducts; there was none in the sinusoids or capsule. There was diffuse amyloid infiltration of the lamina propria of the stomach and upper small intestine.

The changes in the nervous system were restricted to the arachnoid and the peripheral nerves. Amyloid was deposited on the inner surface of the arachnoid (Plate 26, Fig. 10), and extended in an irregular fashion throughout the subarachnoid space, including the prolongations round the optic nerves. The pia mater, the Virchow-Robin spaces, and the central nervous system and its blood-vessels, were not involved. There was slight demyelination of the posterior columns. Amyloid was found scattered haphazard throughout the posterior root ganglia in deposits of irregular size and shape (Plate 26, Fig. 11), some being related to blood-vessels. The ganglion-cells showed all degrees of chromatolysis, and many had disappeared. There was no dendritic proliferation. Nerve-fibres were displaced by the deposits, and showed myelin-sheath degeneration, with proportional axonal destruction, but there was no cellular reaction. The changes in the spinal roots and peripheral nerves were similar, but more severe in the latter. The deposits of amyloid were irregularly scattered through the nerves (compare Plate 26, Fig. 12), and involved both the epineurium and the perineurium. In addition to nodular masses, there was a diffuse infiltration between the fibres. The neurolemmal sheath was not penetrated by the amyloid, but all degrees of destruction of myelin sheaths and axis cylinders existed, and many had disappeared. Although there was no inflammatory cell reaction, those nerves in which degeneration was most advanced showed an excess of collagen fibres and fibroblasts. There was no segmental demyelination or infarction. The amyloid deposits stained with Congo red, but not with methyl violet.

Discussion

Incidence, age, sex, and inheritance. Four cases of primary and 15 of secondary amyloidosis have been found among 22,000 recent admissions to St. Thomas's Hospital, and Symmers (1956*a*) reported 10 cases of each condition in 4,000 post-mortem examinations—an incidence of primary amyloidosis of one in 5,000

and one in 400 respectively. Jones and Frazier (1950) described 14 patients, all Negroes, in 600 consecutive autopsies in adults in West Tennessee, and a similarly high local incidence of the primary form has been reported by Andrade (1952) in Portugal. Of 154 cases of primary amyloidosis, two-thirds began after the age of 50, and of these one-third began in the sixth decade, the extremes of age being nine and 101 years (Rukavina, Block, Jackson, Falls, Carey, and Curtis, 1956). A peculiarity of the disease is the tendency of certain organs to be affected at various ages. Thus the neurological cases in the present series developed at the ages of 30, 32, and 31 years, the others at 54, 57, and 52 years. Cardiovascular amyloidosis is more frequently found in old age, and Hüsselmann (1955) found the majority of his 69 cases in patients over 70 years old. Our neurological cases occurred in men, the others in women, but in larger collected series, with all forms of the disease, about 60 per cent. have been in male patients. Thus Rukavina, Block, Jackson, Falls, Carey, and Curtis (1956) found 61·1 per cent. of male patients in 154 cases; two-thirds of Andrade's (1952) cases of familial polyneuritis, and 60 per cent. of the non-familial cases in the literature, were likewise in male patients. Familial primary amyloidosis has been described by Ostertag (1950–2), Andrade (1952), Kantarjian and de Jong (1953), and Rukavina, Block, Jackson, Falls, Carey, and Curtis (1956). This form affects primarily the nervous system, and the last two groups of authors suggested that it was transmitted as a dominant factor.

Clinical picture. The usual clinical picture is that of an adult who gradually develops symptoms and signs of impaired function of either the myocardium, the peripheral nerves, or the kidneys. The symptoms are progressive and, if the heart or kidneys are involved, death results in a few years. It may be possible to make a clinical diagnosis if the pattern of involvement of organs shows the characteristics about to be described, or if there is involvement of the tongue and skin, but confirmatory biopsy is usually necessary.

The heart. Symmers (1956*a*) reported amyloid involvement of the myocardium in 90 per cent. of 145 cases, and over 50 per cent. of patients with primary amyloidosis develop heart failure (Eisen, 1946). Four of our six patients showed evidence of cardiac damage. Cases 1 and 2 presented cardiac failure; in Case 4 sudden chest pain was followed by cardiac failure and auricular fibrillation, and in Case 6 an electrocardiogram showed myocardial involvement, which was confirmed *post mortem*. In Case 3 there was no clinical or pathological evidence of cardiac involvement, and in Case 5 the heart appeared normal on clinical examination and on electrocardiography. The symptoms and signs are those of progressive myocardial failure. Dyspnoea on exertion is followed by orthopnoea, paroxysmal nocturnal dyspnoea, and oedema. There is tachycardia, often with ventricular ectopic beats, a raised venous pressure, and pulmonary and systemic oedema. The heart may or may not be enlarged but, unless there is associated hypertension, the powerful beat of hypertrophy is absent. Auricular fibrillation is rare, being recorded in only one case out of 16 by Lindsay (1948). Pulsus paradoxus may be present (Couter and Reichert, 1950), and is possibly due to restriction of diastole by amyloid infiltration. The electrocardiogram shows

low-voltage complexes throughout, and radiography reveals either a normal-sized heart or generalized enlargement. The more common causes of heart failure can usually be differentiated. The most important diagnosis to exclude, in view of possible surgical treatment, is constrictive pericarditis. In both conditions there may be pulsus paradoxus, raised venous pressure, a small heart, and a diastolic filling sound, and an identical appearance is found on electrocardiography. Pericardial calcification, or a history of pericarditis, may suggest constriction, but diagnostic thoracotomy may be needed in a patient who is deteriorating. Other myocardial causes of cardiac failure which may give rise to difficulty are myocarditis, 'cardiac hypertophy of unknown origin' (Elster, Horn, and Tuchman, 1955), haemochromatosis, neoplasms, and xanthomatosis.

Blood-vessels. Purpura occurs in at least one-sixth of cases, and other haemorrhagic lesions of the skin, as well as bleeding from the nasopharynx, gastrointestinal tract, and kidneys, are also seen, being probably due to rupture of thickened, inelastic vessels. An unusual event reported by Symmers (1956*b*), and observed by one of us (R. A. C.) in a case not reported here, is the occurrence of bleeding simultaneously from many small, widely separated vessels.

The kidneys. Renal amyloidosis is common, and is present in more than 35 per cent. of cases (Symmers, 1956*a*). The clinical presentations are uraemia, the nephrotic state (Muehrcke, Pirani, Pollack, and Kark, 1955), or simply haematuria. Proteinuria is common and often heavy, and occurs at some stage in 90 per cent. of cases. The protein may be albumin or an abnormal globulin, or both.

The skin is involved in at least 40 per cent. of cases (Eisen, 1946); nodular lesions, generalized thickening, and haemorrhagic lesions (all in Case 2), and generalized pigmentation (Case 3), occurred in the present series. Trophic lesions may be the presenting symptoms of a polyneuritis, and one of our patients (Case 5) initially consulted a dermatologist on this account.

The tongue. Macroglossia is a classical feature of primary amyloidosis, and is obvious in one-third of cases (Dahlin, 1949*a*), and microscopically the tongue is found to be involved in at least 40 per cent. (Symmers, 1956*a*). The mucosa is smooth and waxy, and the enlargement uniform. It may, as in Case 1, cause dysarthria and dysphagia, limit protrusion, and produce swellings under the jaw (Plate 24, Fig. 2; Plate 25, Fig. 6).

The abdomen. Abdominal discomfort occurs in 19 per cent., vomiting in 12 per cent., constipation in 12 per cent., and diarrhoea in 15 per cent. of cases (Rukavina, Block, Jackson, Falls, Carey, and Curtis, 1956). Diarrhoea, with or without constipation, occurs in half the cases of amyloid polyneuritis. At postmortem examination infiltration of the bowel is found, especially of the lamina propria, and explains the symptoms, although infiltration of the nerve-supply may also play a part. The liver is infiltrated in nearly 80 per cent. of cases, and is enlarged in 44 per cent. (Rukavina, Block, Jackson, Falls, Carey, and Curtis, 1956), but jaundice and other signs of disordered liver function (Wollaeger, 1950) are rare. The high incidence of infiltration renders needle biopsy useful. Enlargement of the spleen is rare.

The nervous system. Recent reports (Andrade, 1952; Sullivan, Twitchell, Gherardi, and Vanderlaan, 1955; Kantarjian and de Jong, 1953; Rukavina, Block, Jackson, Falls, Carey, and Curtis, 1956), and the finding of infiltration of the peripheral nerves in 18 of 20 cases of amyloidosis of all types by Ritama and af Björkesten (1954) suggest that amyloidosis of the nervous system occurs more often than has been thought. The best defined syndrome occurs typically in familial cases, but sometimes sporadically, as in Cases 4, 5, and 6, and develops earlier than most cases of primary amyloidosis. In more than half of such cases the initial complaint is of a disorder of sensation in the legs, usually of pain, often of lightning pains. Other initial symptoms are painless ulcers, numbness, hyperaesthesia, weakness of the legs, gastrointestinal disturbances, and impotence. Malaise, loss of weight, or fatigue occurs in all cases. The initial symptoms may be unilateral or bilateral, symmetrical or asymmetrical, but by the time the patient comes to hospital the picture is of a chronically ill man with sensory disturbances and weakness of the legs. Symptoms in the arms are similar, but milder. One-half of the patients complain of diarrhoea or constipation, which sometimes alternate, or of impotence, breathlessness, or oedema. New symptoms may appear abruptly; for example, 'pins and needles' in the fingers were followed by numbness in two days in Case 4, but the usual course is steady progression. The pupils are often irregular and react sluggishly, if at all, to light; later they may be fixed both to light and on convergence. Some wasting and weakness, worse distally and in the legs, are almost invariable, and often severe, but they may, as in Case 5, be so slight as to escape notice for some time. Sensory disturbance is usually extensive, and affects cutaneous rather than deep sensibility, and temperature and pain rather than touch. Complete absence of sensory change (de Navasquez and Treble, 1938) is unusual. The tendon-reflexes may be affected late, the ankle-jerks disappearing first, and the rest as the disease progresses. The combination of severe, stocking-like sensory change and preserved tendon-reflexes led to the diagnoses of hysteria and dermatitis artefacta in Case 5. Some peripheral nerves are likely to be enlarged. Impairment of sweating and dry shiny skin are found in areas of serious sensory disturbance. The flare was everywhere absent from the triple response in Cases 4 and 5, and this result may prove of diagnostic value.

In the cerebrospinal fluid the cells were increased in three reported cases (Findley and Adams, 1948; Kantarjian and de Jong, 1953), and the protein-content in five out of nine sporadic and six of eight familial cases (Andrade, 1952); the highest protein level recorded is 230 mg. per 100 ml. (Kantarjian and de Jong, 1953).

Of the less constant features, the most frequent is alteration of the voice, due to macroglossia, to laryngeal palsy, or to amyloid deposits in the vocal chords. Impaired vision, due to intraocular deposits, and deafness are also seen. Vitreous deposits occur relatively often in association with polyneuritis (Kantarjian and de Jong, 1953; Rukavina, Block, Jackson, Falls, Carey, and Curtis, 1956). Isolated facial and hypoglossal palsies, and sphincter disturbances, including both retention and incontinence, have been reported. Brief attacks of unconsciousness

were described by Andrade (1952) and by de Bruyn and Stern (1929); they occurred in Case 6, and were possibly due to hypoglycaemia.

Diagnosis of amyloid neuropathy. The diagnoses made in Cases 4, 5, and 6 at various hospitals illustrate the difficulties: chronic tonsillitis, dermatitis artefacta, hysteria, malingering, disseminated sclerosis, spinal tumour, tabes dorsalis, and leprosy. Amyloid polyneuritis may mimic tabes. Although doubts of the latter diagnosis may be aroused by the symmetrical motor symptoms and by the absence of spincter disorders, examination of the blood and cerebrospinal fluid may be essential. The greatest difficulty lies in distinguishing amyloid from other types of polyneuritis. If leprosy is likely, the social consequences make biopsy essential. Sensory radicular neuropathy is similar in many respects, including the family history and, sometimes, diarrhoea and abnormal pupils, but wasting and weakness, and enlarged peripheral nerves, both characteristic of amyloid polyneuropathy, are usually absent. Déjèrine and Sottas's disease closely resembles amyloid polyneuritis, and may be distinguished from it by nystagmus and (often) cerebellar signs, by the uniform affection of the motor and sensory fibres, and by the absence of gastrointestinal, sexual, and other visceral symptoms. Enlarged peripheral nerves are found in both conditions, but have not been emphasized in amyloidosis, although they were found in all our neurological cases. Minor enlargement and undue firmness are hard to evaluate, for the size of a nerve varies from person to person, and the ease with which it is seen or felt varies with the obesity of the patient. In any chronic polyneuritis there is often an increase in connective tissue and slight enlargement. Marie (1906) and Boveri (1910) stipulated visibly enlarged nerves before progressive hypertrophic polyneuritis could be diagnosed. In our cases some nerves were undoubtedly abnormal, being thick and tendinous, but others supplying affected areas were palpable but not definitely abnormal, and in Case 4 a nerve leading to an unaffected area was clearly enlarged. In some familial cases of peroneal muscular atophy (England and Denny-Brown, 1952) there are peripheral wasting, severe sensory changes, and trophic lesions, but the absence of visceral disorders and the early and severe affection of the peroneal muscles distinguish the condition from amyloid neuropathy. Furthermore, the sensory disturbance is originally of radicular distribution, affecting pain rather than temperature, the pupils are normal, and the nerves not enlarged. Cases of amyloid polyneuritis and of sensory radicular neuropathy have been reported as familial lumbo-sacral syringomyelia, on account of the extensive disturbance of appreciation of pain and temperature. The strict symmetry, onset in the distal extremity of the limbs, and visceral symptoms, should cast doubt on a diagnosis of syringomyelia.

Investigations of diagnostic help are serum-protein examination, the Congo-red tests, and biopsy. The erythrocyte sedimentation rate may be raised, but is often normal, especially in neurological cases. Serum-protein changes include diminished total protein, diminished albumin, increased globulin, and the finding on electrophoresis of an abnormal protein, which may appear in the urine, in the region of the α_2–β globulin bands. In five of our patients the total protein-

content and the albumin-content were reduced or at the lower limit of normal, and Rukavina, Block, Jackson, Falls, Carey, and Curtis (1956) found hypoproteinaemia and hypoalbuminaemia in 29 of 47 reported cases. Our cases did not show the increase of globulin found in 29 of their patients. Serum electrophoresis was performed in four cases. In Cases 4 and 5, both with neuropathy, the strip was normal. In Case 1 a clearly defined abnormal band was seen between the α_2- and β-globulin bands, and in another patient with neuropathy (Case 6) excess of protein was seen in the region of the β-globulins. The diagnostic value of electrophoresis is reduced by technical difficulties; for example, repeated strips had to be made in Case 1 to establish the presence of the abnormal band. Nevertheless its results are thought to be significant, for Block, Rukavina, and Curtis (1956) found electrophoretic abnormalities in 29 out of 56 members of an affected family, of whom 15 showed an atypical peak and 14 showed 'poor resolution' in the α_2–β globulin region. All affected members had electrophoretic abnormalities and, of the unaffected members who had such abnormalities, the majority were less than 18 years old. The authors suggested that these abnormalities might foreshadow the onset of the disease.

The Congo-red test was performed in three of our patients. The result was positive in Case 3, equivocal in Case 1, and negative in Case 6; we have accepted 90 per cent. retention of dye in one hour as positive. The result probably depends on the amount of amyloid and its affinity for Congo red and, although a negative result is of no significance, falsely positive results are rare. Reactions, except with repeated injections, are uncommon, and have been related to particular samples of Congo red (Kark, 1955); but the test should not be done in patients with cutaneous amyloidosis, lest permanent staining should occur. Recently attempts have been made to devise a test using the uptake of radioactive iodine as a measure of amyloid deposition (Burchell, 1954). Although some cases have shown an increased extrathyroidal uptake due to absorption by amyloid, other cases have failed to do so. This result would be expected, as some varieties of amyloid fail to combine with iodine.

Biopsy is still the most reliable diagnostic test. Many tissues have been selected, including in the present cases skin, gum, liver, skeletal muscle, and peripheral nerve. Skin lesions are the easiest and most reliable source for biopsy, and if only a small amount of amyloid is present it may be found in the walls of small vessels, in the arrectores pilorum, and on the walls of subcutaneous fat-cells. A palpably abnormal cutaneous nerve leading to a seriously affected part should be selected for peripheral nerve biopsy, and it is useful to remove a piece of skin and muscle through the same incision. Aspiration liver biopsy is of great value, but it is possible to overlook slight infiltration, as in Case 1. The earliest change is usually a thickening of the basement-membranes of the sinusoidal capillaries, and in a section stained by routine methods there may be little tinctorial difference between this thickened membrane and the adjacent cytoplasm (Plate 24, Fig. 4). Occasionally the portal tracts alone may be involved, and needle biopsy may fail to reveal the condition. All sections should be stained with Congo red and methyl violet in addition to the usual methods.

Clinical diagnosis. The illness may present a large variety of symptoms, but is characterized by the occurrence in adult life of a chronic progressive illness, without significant fever or other evidence of toxaemia to explain the constant complaint of fatigue, malaise, or loss of energy or weight. Usually complaint is made directing attention to one or other organ, and the clinical problem is one of system diagnosis. There may be diagnostic signs in the organ primarily involved, but evidence of involvement of other systems should be sought. For example, Case 1 presented cardiac failure, macroglossia, and proteinuria; Case 2 cardiac failure, macroglossia, cutaneous changes, and proteinuria; Case 3 malaise, oedema, pigmentation, proteinuria, and dyspnoea possibly due to pulmonary amyloidosis; Case 4 monoarthritis, malaise, and polyneuritis; Case 5 polyneuritis, diarrhoea, impotence, vocal changes, and malaise; Case 6 polyneuritis, diarrhoea, and vitreous opacities. The course of the illness is also of diagnostic value: the appearance of new signs, and resistance to treatment, as in Cases 4 and 6, may suggest the diagnosis.

Prognosis. Death usually occurs within one to five years, the average in 154 cases being 26 months (Rukavina, Block, Jackson, Falls, Carey, and Curtis, 1956). The duration of the illness is shortest in patients with renal or cardiac involvement. The longest recorded survival in cardiac amyloidosis is 14 years (Koletsky and Stecher, 1939), and in patients with neurological symptoms over 20 years (Kantarjian and de Jong, 1953). The course of the disease is uninfluenced by treatment.

Pathology. The distinctions formerly drawn between primary and secondary amyloidosis, on the grounds of the different organ distribution, are now regarded as invalid. More thorough examination has shown that sites usually involved in primary amyloidosis may also be affected in the secondary form (Symmers, 1956*a*) though the incidence may be very different. The unity of all forms of amyloidosis was further supported by Meyer-Arendt (1952), who showed that all amyloid gave a similar ultraviolet microspectrograph. Among the conditions that influence the distribution of amyloid in certain sites are chronic sepsis, genetic factors, and senescence. In secondary amyloidosis due to chronic sepsis the distribution is restricted mainly to the spleen, kidneys, adrenals, and liver. In amyloid neuropathy there may be a familial history, and the deposits are initially localized to peripheral nerves, but later may spread elsewhere. In old age deposits of amyloid may be entirely limited to the heart. Some of the unusual sites of amyloid deposition may be explained by the observations of Dahlin (1949*b*) and Missmahl and Hartwig (1953–4), who showed its relation to reticulin and to collagen respectively. These findings recall the views of Mallory (1914) and Warren (1930) that amyloidosis was due to perverted activity of fibroblasts.

Only the more unusual features of the present cases are discussed; these included deposition on the cell-membrane of periadrenal fat-cells in Case 6, and deposits of amyloid in the adrenal capsule, with sparing of the gland, in Case 1. In Cases 1, 2, and 6 amyloid was deposited on the surface of the myocardial fibres and in the interstitial tissues of the heart. Pulmonary amyloidosis was

widespread in Case 3. The deposits were found in all lobes, in patches of varying size separated by normal lung. They occurred around branches of the pulmonary arteries and veins, and on the basement-membranes of the alveolar capillaries. The elasticity of the affected lung was reduced, and it seemed probable that gaseous diffusion had been impeded. Amyloid deposits in the brain are almost unknown, although they have been found after irradiation of the brain (Fischer and Holfelder, 1930), in neurones in Alzheimer's disease (Divry, 1934), and in the cerebral vessels and meninges (Divry, 1936, 1941–2). Meningeal involvement was found in Cases 2 and 6. Deposits in the peripheral nerves are commoner; Ritama and af Björkesten (1954) found them in 18 of 20 cases of amyloidosis, including both primary and secondary forms, and they were present in five of our cases. Amyloid deposits in a nerve may cause no recognizable clinical signs, but some obscure symptoms reported in earlier cases were probably due to this cause. The disturbance of neural function has usually been attributed to ischaemic axonal damage by intraneural deposits. Although excess of endoneural collagen was found in Cases 4 and 5, and may have resulted from ischaemia, no infarcts or segmental demyelinization were found. Kinking of nerve fibres (Plate 26, Fig. 12) was the more likely explanation of the loss of nerve function. The histological diagnosis has to exclude sensory radicular neuropathy and progressive hypertrophic polyneuritis. In the former disease 'amyloid' deposits have been found occasionally in the posterior root ganglia (Denny-Brown, 1951), but the absence of amyloid elsewhere, together with subcapsular dendritic proliferation, distinguishes the condition from amyloid polyneuritis. In progressive hypertrophic polyneuritis, which has been confused in the past with amyloid neuropathy (de Navasquez and Treble, 1938), the nerve-fibres are enclosed in multinucleated hyperplastic neurolemmal and endoneural sheaths grouped in bundles (Austin, 1956), but the perineurium and epineurium are often normal, and amyloid is absent.

Although amyloid is regarded primarily as an extracellular disorder, intracellular deposits have been found occasionally in human primary amyloidosis in the kidney, liver, and muscle. In Case 1 such deposits were responsible for causing macroglossia, and involved other skeletal muscles; in Case 2, however, interstitial deposits, which are the more usual finding, were the cause of the macroglossia. Intracellular amyloid in muscle first appears in relation to the myofibrils in otherwise normal fibres (Symmers, 1956*a*); the deposits enlarge, coalesce, and cause fibre distension. Less severely damaged fibres retain transverse striations, which are lost as the process develops. Later a longitudinal fibrillary change occurs in the sarcoplasm as the fibre fills with amyloid (Plate 24, Fig. 5); the sarcolemmal nuclei disappear, and the fibres appear to be dead, but to have excited no cellular reaction. The changes do not suggest that amyloid deposition occurs only in dying cells.

Although all forms of amyloid are closely related, the variable staining reactions indicate that it is not of constant composition, but varies slightly from one case to another. Since the first description by von Rokitansky (1842), a great deal of chemical and experimental research has been directed to elucidating the

pathogenesis of the condition, and a summary of the more important findings has been given by Rukavina, Block, Jackson, Falls, Carey, and Curtis (1956). Much time has been spent in investigating the quantitative and qualitative changes in the blood-proteins and the composition of amyloid. Most cases of amyloid disease are associated at some time with altered blood-protein levels, and Dick and Leiter (1941) showed that plasma-proteins often decrease as amyloid is deposited. More recently interest has been focused on the relationship between dysproteinaemia and immune reactions. Mellors and Ortega (1956) demonstrated γ-globulins fixed to glomerular capillary walls in a human case of amyloidosis following drug sensitivity, and Letterer (1949) has reviewed the relationship between hyperglobulinaemia and antigen-antibody reactions. The deposition of amyloid in relation to reticulin and collagen fibres has been confirmed by Missmahl and Hartwig (1953–4), who showed by the use of polarized light that masked collagen fibres could be traced in the amyloid deposits. Pirani, Bly, and Sutherland (1950), however, attributed amyloid formation to an alteration in the ground-substance around fibres and cells, and cited its experimental production in the scorbutic state. The localization of some antigen-antibody reactions on the surface of fibres may be the factor which will eventually reconcile the anatomical deposition of amyloid on fibres and cell-membranes with the view that amyloidosis is related to an antigen-antibody disorder.

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Summary

1. Six cases of generalized primary amyloidosis are reported, and the condition is discussed.

2. Approximately two-thirds of all cases occur in men, and the clinical form is partly related to age, neuropathy occurring relatively early and cardiac myopathy relatively late.

3. The clinical picture varies, but frequently shows the gradual onset without fever or toxaemia, in adult life, of impaired function of the myocardium, kidneys, or peripheral nerves. The illness is progressive despite treatment and, if the heart or kidneys are involved, leads to death in a few years.

4. The polyneuritis affects first and most severely the longest fibres. The symptoms are predominantly sensory, and usually the first symptom is pain, often lightning pains. The motor signs are those common to all types of chronic

polyneuritis, and may be of any severity. The characteristic sensory abnormality is diminished appreciation of temperature and pain. The ankle-jerks, and later the other tendon-reflexes, are lost, but they may be present when symptoms and cutaneous sensory signs are advanced. Additional clinical features include diarrhoea, impotence, vitreous opacities, abnormal pupils, and thickened peripheral nerves.

5. The diagnostic value of the Congo-red test, electrophoresis of plasma and urinary proteins, radioactive iodine uptake, and biopsy, is discussed.

6. Some of the unusual features of the morbid anatomy, and the pathogenesis, are discussed. It is concluded that amyloidosis, whether primary or secondary, is a single disease process, with variations in distribution determined by such factors as inheritance, age, and sepsis.

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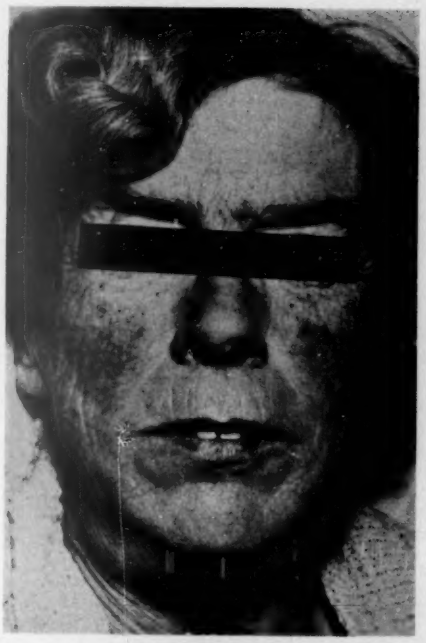

FIG. 2. Case 1. Submandibular swellings due to macroglossia

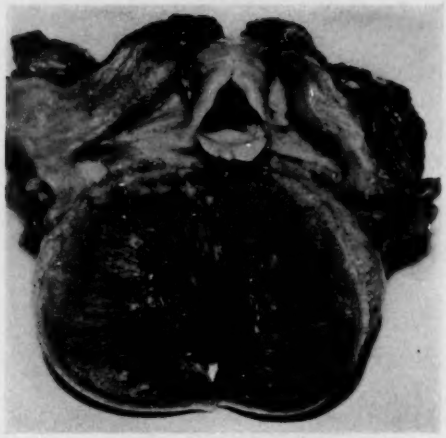

FIG. 3. Case 1. The macroscopic appearance of the tongue

FIG. 4

FIG. 5

FIG. 4. Case 1. Section of liver, to show thickening of basement-membranes. The photograph was taken with filters to exaggerate the difference between cytoplasm and amyloid (haematoxylin and eosin, × 500)
FIG. 5. Case 1. Section of tongue, to show amyloid deposits within muscle-fibres adjacent to normal fibres (haematoxylin and eosin, × 280)

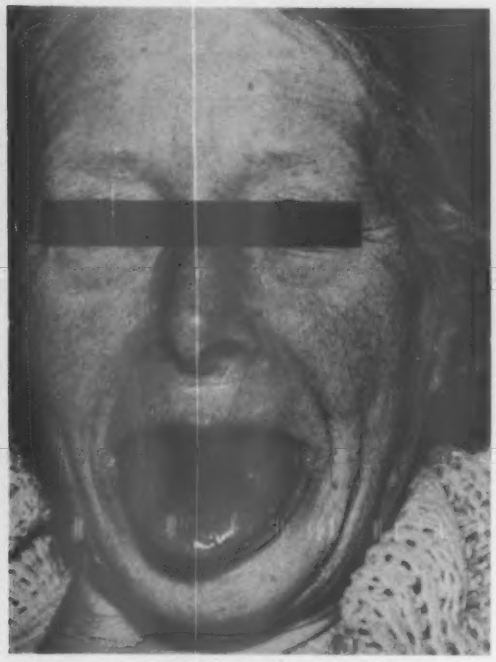

FIG. 6. Case 2. Great enlargement of the tongue

FIG. 7. Case 2. Nodular cutaneous lesions

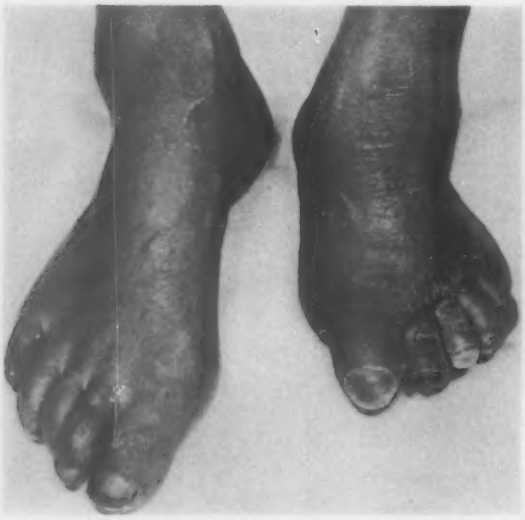

FIG. 8. Case 4. Trophic changes in left foot

FIG. 9. Case 5. Thickened musculo-cutaneous nerve of leg

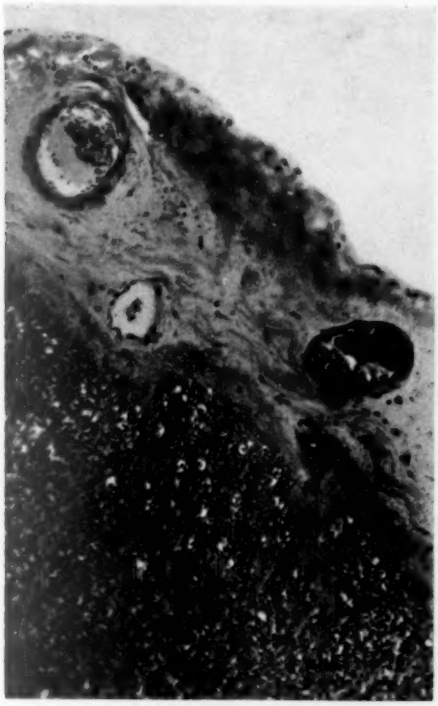

FIG. 10

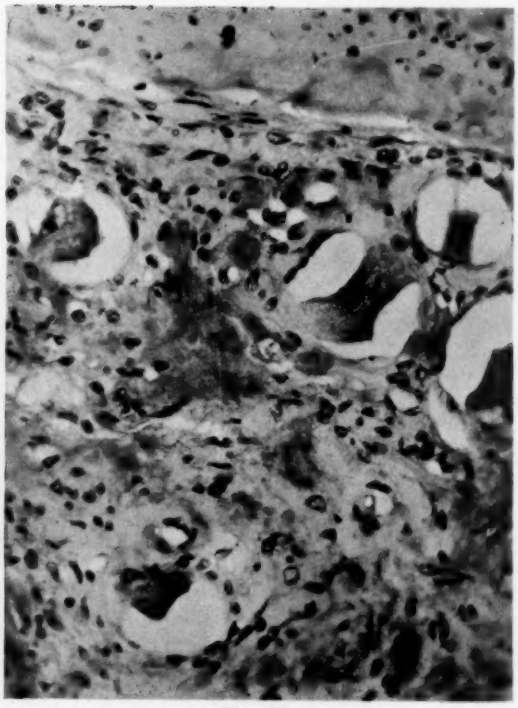

FIG. 11

FIG. 10. Case 6. Subarachnoid deposits of amyloid (haematoxylin and eosin, × 42)
FIG. 11. Case 6. Posterior root ganglion, to show amyloid deposits and degeneration of nerve-cells (haematoxylin and eosin, ×200)

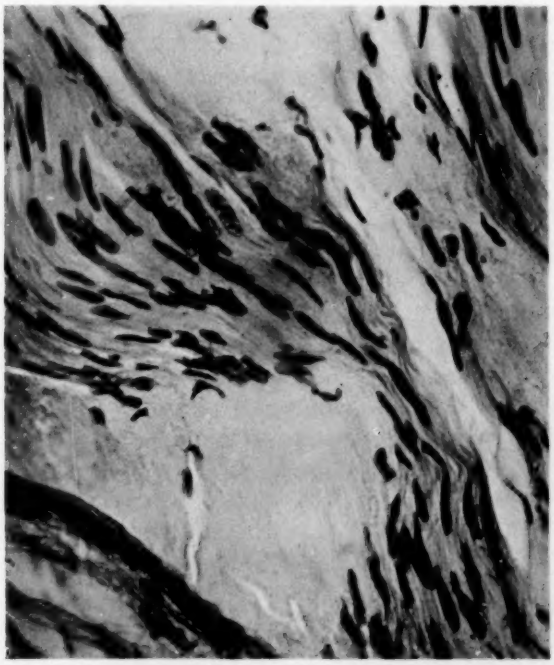

FIG. 12. Case 5. Section of peripheral nerve, to show amyloid deposit and compression and kinking of fibres (haematoxylin and van Gieson, ×500)

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ASPIRATION OF FOOD AND VOMIT[1]

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With Plates 27 to 29

THE danger of choking while eating is common knowledge, and many cases of aspiration of food into the lungs have been recorded. The greater danger of choking while vomiting is less widely recognized and more sparsely documented, probably because it often takes place unobserved.

Historical Survey

Aspiration of food or drink

Since classical times the danger of suffocation from food or drink entering the lungs has been recognized. Hippocrates (*c.* 400 B.C.) warned his hearers that 'for drinking to provoke a slight cough, or for swallowing to be forced, is bad'. Anacreon, the Greek poet, is said to have died in 475 B.C. from inhalation of a grape seed (Paris and Fonblanque, 1823*a*). It is also recorded that during a feast at Winchester in A.D. 1053 Edward the Confessor accused Godwin, Earl of Wessex, of having murdered Alfred the Etheling. Godwin, protesting his innocence, said 'If I am guilty may this bread choke me'. He ate the bread, fell down in a fit, and died. More recently, in 1583, the English poet Humphrey Gilbert choked and died with a piece of mutton in his glottis. John Hunter was aware that drinks could be aspirated into the lungs, for he stated in 1781, while giving evidence at the trial of Captain John Donellan for the murder of Sir Theodosius Broughton: 'It is in the mouth of everybody that a little brandy will kill a cat. I have made the experiment; in all those cases where it kills the cat, it kills the cat by getting into her lungs, not her stomach.'

It is a matter of common sense that aspiration will occur if attempts are made to feed unconscious patients; Pridie (1862–3) told of such an occurrence in a boy in Newcastle, who was 'threatened with syncope' during an anaesthetic and died while an attempt was being made to pour brandy down his throat. That aspirations are particularly prone to occur in pharyngeal paralysis was shown experimentally in animals by Mendelssohn (1845), and recognized clinically in diphtheria by Morrisseau (1851) and West (1866). Nélaton (1876) remarked that food aspiration was common in the aged or moribund, in coma, and in diphtheritic paralysis. Wilks and Moxon in 1889 observed that such accidents

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were common in cerebral disease, especially in softening of the pons. Cohnheim (1890) was also aware of the danger in those whose 'laryngeal depressors' were paralysed. Bradford, Bashford, and Wilson (1918–19), in their classical paper on infective polyneuritis, recorded the association of lung complications with dysphagia; but in poliomyelitis the great danger of aspiration has only recently been generally recognized (Lenarsky, Parr, and Seanor, 1951; Jurow and Dolgopol, 1953; Espir, Dominian, and Russell, 1956). On the other hand, aspiration pneumonia is not always the result of pharyngeal palsy; it occurs, for example, in oesophageal obstruction, and may be the first sign of such disease (Belcher, 1949).

Aspiration in infants. That major aspiration of milk may occur in healthy infants and be lethal was recognized by Marie, who coined the term 'milk embolism' (Marie, Seringe, and Hebert, 1947). Many further examples have since been published (Ribadeau Dumas and Héraux, 1950; Debré, Grumbach, and Caron, 1951; Bouchet, Zha, and Henault, 1954; Imbert, Chevallier, Treppoz, and Sebbah, 1955). Such accidents, of course, are more likely to occur when the infant is comatose; an example occurring during chlorpromazine therapy was reported by Jeune, Carron, and Bianco in 1955.

That repeated minor aspirations also occur was recognized by Guieysse-Pellissier (1920), and resulting lipoid pneumonia was described by Pinkerton (1927) and by Pierson (1932). The experiences of Hug (1942), and the experiments of Moran (1953*b*), indicate that such aspirations may result from careless bottle-feeding and may be one of the causes of interstitial plasma-cell pneumonia in infants. Everyone who has the care of infants is aware of the frequent coughing and choking during feeds. Such coughing is the result of milk reaching the air passages. The fact that serious effects seldom follow may be explained by the observation of Moran (1953*a*) that the noxiousness of inhaled fluids varies with the sugar-content; milk containing little sugar is therefore relatively bland, whereas synthetic feeding stuffs are more harmful and liable to produce pulmonary oedema.

Minor aspirations in adults. It is common experience that food may 'go down the wrong way', and that this often happens during the feeding of the ill, aged, and infirm. The audible and auscultated bubblings when such patients are being fed with feeding cups indicate that such ministrations are often more asphyxiating than nourishing. Confirmation of this fact was given by Fetterman and Moran (1942) who, by studying the histology of food particles, were able to recognize them in association with inflammatory changes in the lungs in 27 (5·7 per cent.) of 469 consecutive autopsies conducted on patients from medical wards. They concluded that many cases of terminal bronchopneumonia in aged and feeble medical patients could be attributed to aspiration pneumonia.

Minor aspirations of food in animals. Innes, Yevich, and Donati (1956) were puzzled by the appearance of fragments of bone in the lungs of small laboratory animals. They found that the bone came from the food, which contained 5 per cent. of fish meal. Such fragments were found in the lungs of one dog, and of 44 out of 750 rats (5·9 per cent.).

Aspiration of vomit

Animals. An instance occurring in a calf with an under-developed epiglottis was quoted by Boneti in 1700. Evidently such happenings in animals are not uncommon, for Paris and Fonblanque (1823*b*) reported that an inquiry among carcase butchers revealed that the presence of food in the pulmonary passages was by no means a rare occurrence in animals which had been struck on the head.

Infants and children. Boneti (1700) mentioned this accident in a child aged three years, Parrot (1868) recognized it as a clinical entity, and von Hüttenbrenner (1877) thought it was a not uncommon cause of sudden death in infants. An indication of its incidence in the newborn was given by Rhaney and MacGregor (1948), who reported 41 cases encountered at autopsy among 962 infants. Three-quarters of the infants who had aspirated vomit were premature, and nearly half had intracranial haemorrhage. De Robert and Hadengue (1949), with experience of a large number of cases, emphasized the fact that such aspiration is one of the commonest causes of death in children under two years. It frequently remains undiagnosed at autopsy because the main airways are clear; only if the small bronchi are opened up, and their contents carefully studied, does the diagnosis become apparent.

Adults. Senility, like immaturity, is a potent factor in such aspirations; Polson (1955) recorded death from this cause in a woman of 88, who was in hospital with fractured femur. She appeared well, but while enjoying lunch suddenly collapsed and died. It seems that anything that interferes with the pharyngeal reflexes predisposes alike to aspiration of food and to aspiration of vomit.

Intoxication. As might be expected, aspiration frequently takes place during alcoholic intoxication, when vomiting occurs while the laryngeal reflexes are depressed (Paris and Fonblanque, 1823*b*). Such a case was recorded by Laennec (1819): his friend Professor Corvisart, wishing to check unexpectedly on a concierge in the hospital, entered his room; the man, who had been drinking and felt nauseated, in making a violent effort not to vomit fell dead at the professor's feet. Autopsy showed the larynx, trachea, and bronchi to be filled with partly digested food. Mérat (1874) quoted two similar cases, one of which concerned a porter in the same hospital, who had been drinking heavily in the evening and was found dead in the morning. Mérat stated that Professor Corvisart had encountered many such examples of death from aspiration of vomit. Similar cases were also recorded by Skae (1840), Jackson (1844), Porter (1856), Piégu (1868), Geschwind (1881), and Langgaard (1887), and are recognized by most pathologists who are experienced in medico-legal work. It is certain that alcohol is not the only toxin that predisposes to such aspirations; they have been reported in the toxaemia of gangrene (Matthews, (1850)), and are common in diabetic coma.

Epilepsy and insulin shock therapy. Aspiration of gastric contents is a major cause of death during epileptic fits, and may pass unrecognized, for vomit need

not appear at the lips (Alcock, 1821; Foville, 1869; Matthews, 1850). In infantile convulsions 40 per cent. of children vomit during or after the fit, and it is estimated that at least half of those who die do so after inhaling vomit (Ounsted, 1956). Psychiatric practice provides further examples occurring during insulin shock therapy (O'Neill, 1938). The majority of such cases present pulmonary oedema, which occurs in about one per cent. of such patients (Gralnick, 1944). The cause of such oedema is seldom understood (Nielsen, Ingham, and von Hagen, 1938; Furst, 1940).

Anaesthesia. Death from this cause during anaesthesia has long been recognized. In Sansom's (1861) review of the first 51 reported cases of death under chloroform, there were two that followed sudden vomiting. A further case was reported by Balfour (1862–3). During the Burmese war of 1853 a soldier was anaesthetized with chloroform shortly after his dinner. The femoral artery was tied, but during the operation the patient vomited, and died shortly afterwards. At autopsy the trachea was found to be filled with vomit. It is still insufficiently realized that such aspirations may occur in spite of several hours of starvation. The first experimental approach to this problem of anaesthesia was that of Mendelson (1946), who stressed the fact that aspiration of only small amounts may be fatal. Merrill and Hingson (1951), by means of questionnaires, ascertained 59 maternal deaths from this cause among 42,439 deliveries; they calculated that two maternal deaths in every 100 in the United States were due to aspiration of vomit. Weiss (1950) and Culver, Makel, and Beecher (1951) investigated the regurgitation of gastric contents during 300 anaesthetics after introducing Evans's blue dye into the stomach. Regurgitation occurred in 26 per cent. of cases, and aspiration into the lungs in 16 per cent., but no inflatable cuffs were used on the intratracheal tubes. They made a plea for the use of stomach tubes of large bore. In a recent investigation by the Association of Anaesthetists into 1,000 deaths associated with anaesthesia, 110 were ascribed to aspiration of vomit (Edwards, Morton, Pask, and Wylie, 1956). The authors recognized the difficulty of pathological diagnosis, and placed cases in this category only when the clinical history justified it. Most of the fatalities were the result of failing to ensure that the stomach was empty at the time of operation; in several instances the aspiration occurred during post-anaesthetic vomiting. These authors, and Parker (1954), mentioned pulmonary oedema as a common feature in such cases.

Hypnotics and emetics. That emetics sometimes prove lethal is shown by the following three cases.

A healthy eight-months-old boy was given a small dose of castor oil; 'he swallowed it, but then suddenly stretched out his tongue, turned livid, he did not struggle, scarcely a sound passed from him and he was dead' (West, 1859).

A woman telephoned to her doctor asking for advice about her husband, who was in pain from a duodenal ulcer. The doctor advised sodium bicarbonate; the patient drank a pint of the solution, vomited, and died. At autopsy the only significant finding was vomit in the lungs (Sladden, 1954).

A middle-aged man was in pain from acute appendicitis. He was given one-third of a grain of morphine and sent to hospital, where he vomited in the

Casualty Department, and died almost immediately. Autopsy confirmed the presence of vomit in the airways (Bruce, 1955). It is understandable that drugs with both hypnotic and emetic actions, such as morphine, should predispose to such aspirations.

Violence. Physical violence can occasionally cause aspiration of vomit.

Two factory workers were wrestling in a friendly way. They fell, and one, aged 50, appeared to die at the moment of falling. In a very detailed autopsy, the only abnormality found was vomit in both large and small bronchi (Behrend, 1868).

During a game of Rugby football a boy, aged 16, was tackled and fell. He remained crouching, and was having difficulty in breathing. He was taken off the field, and soon died. At autopsy the air passages contained gastric contents. Similar instances of choking and death have been recorded during rape and sodomy (Polson, 1955).

Fright may sometimes cause vomiting and aspiration, as in the following case reported by Smyth in 1874. After incision of an abscess in the neck of a timid boy, aged four, the child coughed and choked, and subsequently died in spite of tracheotomy. At autopsy, in the presence of the boy's father, part-digested meat was found blocking the bronchi. Another example was mentioned by Brouardel (1897): a 20-months-old child had been drinking sugar and water, and was crying on the nurse's lap. The father shouted 'Will you be quiet, you ugly little monkey', whereupon the child drew a deep breath, and died immediately. Autopsy showed the stomach and airways to be full of the same sticky fluid.

Entry of Gastric Contents into the Lungs after Death

In most of the cases quoted above the evidence of ante-mortem aspiration of vomit is circumstantial. Autopsy findings in this condition are often inconclusive, because gastric contents may reach the bronchi after death (sometimes giving them a reddish or gangrenous appearance (Parrot, 1873; Wilks and Moxon, 1889; Delafield and Prudden, 1936)). Proper appreciation of this possibility is essential when interpreting morbid anatomical appearances in the lungs, and it is remarkable that the subject has hitherto received so little attention.

Investigation. Barium sulphate, in quantities of six to 10 ounces of suspension, was introduced immediately after death through stomach-tubes into the stomachs of 10 patients. The tubes were then removed, and the bodies sent to the mortuary in the usual way. At autopsy 24 to 48 hours later radiographs were taken of the lungs. Barium was found in the lungs of seven of the 10 bodies and, surprisingly, it had in some cases even reached the alveoli, presumably as the result of manipulation of the lungs during their removal. Fig. 1 (Plate 27) shows a typical example.

Conclusion. The presence of gastric contents in the lungs at autopsy, often ascribed to ante-mortem or agonal aspiration, is not in itself conclusive evidence of such a happening unless, immediately after death, and before moving the body, the trachea has been blocked with an obturator. In the following investigation Foley catheters were used for this purpose.

Aspiration of Food and Vomit During Life

This problem was investigated in a consecutive series of 94 adult male and

not appear at the lips (Alcock, 1821; Foville, 1869; Matthews, 1850). In infantile convulsions 40 per cent. of children vomit during or after the fit, and it is estimated that at least half of those who die do so after inhaling vomit (Ounsted, 1956). Psychiatric practice provides further examples occurring during insulin shock therapy (O'Neill, 1938). The majority of such cases present pulmonary oedema, which occurs in about one per cent. of such patients (Gralnick, 1944). The cause of such oedema is seldom understood (Nielsen, Ingham, and von Hagen, 1938; Furst, 1940).

Anaesthesia. Death from this cause during anaesthesia has long been recognized. In Sansom's (1861) review of the first 51 reported cases of death under chloroform, there were two that followed sudden vomiting. A further case was reported by Balfour (1862–3). During the Burmese war of 1853 a soldier was anaesthetized with chloroform shortly after his dinner. The femoral artery was tied, but during the operation the patient vomited, and died shortly afterwards. At autopsy the trachea was found to be filled with vomit. It is still insufficiently realized that such aspirations may occur in spite of several hours of starvation. The first experimental approach to this problem of anaesthesia was that of Mendelson (1946), who stressed the fact that aspiration of only small amounts may be fatal. Merrill and Hingson (1951), by means of questionnaires, ascertained 59 maternal deaths from this cause among 42,439 deliveries; they calculated that two maternal deaths in every 100 in the United States were due to aspiration of vomit. Weiss (1950) and Culver, Makel, and Beecher (1951) investigated the regurgitation of gastric contents during 300 anaesthetics after introducing Evans's blue dye into the stomach. Regurgitation occurred in 26 per cent. of cases, and aspiration into the lungs in 16 per cent., but no inflatable cuffs were used on the intratracheal tubes. They made a plea for the use of stomach tubes of large bore. In a recent investigation by the Association of Anaesthetists into 1,000 deaths associated with anaesthesia, 110 were ascribed to aspiration of vomit (Edwards, Morton, Pask, and Wylie, 1956). The authors recognized the difficulty of pathological diagnosis, and placed cases in this category only when the clinical history justified it. Most of the fatalities were the result of failing to ensure that the stomach was empty at the time of operation; in several instances the aspiration occurred during post-anaesthetic vomiting. These authors, and Parker (1954), mentioned pulmonary oedema as a common feature in such cases.

Hypnotics and emetics. That emetics sometimes prove lethal is shown by the following three cases.

A healthy eight-months-old boy was given a small dose of castor oil; 'he swallowed it, but then suddenly stretched out his tongue, turned livid, he did not struggle, scarcely a sound passed from him and he was dead' (West, 1859).

A woman telephoned to her doctor asking for advice about her husband, who was in pain from a duodenal ulcer. The doctor advised sodium bicarbonate; the patient drank a pint of the solution, vomited, and died. At autopsy the only significant finding was vomit in the lungs (Sladden, 1954).

A middle-aged man was in pain from acute appendicitis. He was given one-third of a grain of morphine and sent to hospital, where he vomited in the

Casualty Department, and died almost immediately. Autopsy confirmed the presence of vomit in the airways (Bruce, 1955). It is understandable that drugs with both hypnotic and emetic actions, such as morphine, should predispose to such aspirations.

Violence. Physical violence can occasionally cause aspiration of vomit.

Two factory workers were wrestling in a friendly way. They fell, and one, aged 50, appeared to die at the moment of falling. In a very detailed autopsy, the only abnormality found was vomit in both large and small bronchi (Behrend, 1868).

During a game of Rugby football a boy, aged 16, was tackled and fell. He remained crouching, and was having difficulty in breathing. He was taken off the field, and soon died. At autopsy the air passages contained gastric contents. Similar instances of choking and death have been recorded during rape and sodomy (Polson, 1955).

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Aspiration of Food and Vomit During Life

This problem was investigated in a consecutive series of 94 adult male and

female patients in two surgical wards, who either had undergone major surgery or were debilitated for other reasons. No study was made of aspiration during surgical operations.

First experiment

Method. During the period of observation, usually two to four days, microcrystalline non-flocculable barium sulphate was added to all drinks, in a proportion of one part in six. Radiographs were taken (usually with portable machines) daily, or more frequently if aspiration was suspected. This barium suspension proved fairly palatable when diluted with 'ribena' or other fruit juice, although it tended to leave a coating in the mouth afterwards. No untoward effects were encountered. When inhaled, barium sulphate seemed likely to prove more bland to the lung than the accompanying organic food particles. Moreover, being radio-opaque, it could be detected, and appropriate measures taken to deal with the aspiration which otherwise would have passed unnoticed.

Results. Of these 94 patients, barium reached the lungs in 10, whose case histories are summarized below. It was unusual for the presence of barium to be suspected clinically. In nine cases the barium was demonstrated radiographically, but in one case it was seen only on bronchoscopy.

Case 1 (R.I. 8951). A man aged 47 underwent emergency gastrectomy on 6.1.54 for bleeding duodenal ulcer, and made a good recovery. Barium at the base of the right lung (Plate 27, Fig. 2) was a chance finding three days after operation. Since the stomach was being aspirated intermittently, and the patient did not vomit, it is probable that the barium entered the lungs during feeding.

Case 2 (R.I. 183539). A woman aged 68 underwent laparotomy on 20.11.53 for carcinomatosis arising from carcinoma of the cervix. Barium appeared at the base of the right lung on three occasions, 11, 14, and 22 days after operation. The patient was feeble, vomiting, and drowsy with narcotics. It was impossible to say whether food or vomit was aspirated. Radiographs of the lungs *post mortem* confirmed the presence of barium.

Case 3 (R.I. 184078). A man aged 70 had an operation on 29.11.53 for repair of a strangulated inguinal hernia. Congestive heart failure was present. Bronchoscopy was necessary four days after the operation to clear his airways. Barium was present in the right main bronchus, but there was not enough to show up on a radiograph of the chest. He died four days later.

Case 4 (R.I. 183745). A male lunatic, aged 73, had dysphagia for one month due to carcinoma of the oesophagus. The stricture was dilated by bougie with relief of the dysphagia. Barium was then given with his food for three days. The patient aspirated barium on several occasions (Plate 28, Fig. 3). There was no suggestion of an oesophageal fistula.

Case 5 (R.I. 118563). A man aged 72, an alcohol addict, underwent vagotomy and partial gastrectomy for pyloric stenosis on 29.1.54. Two days after operation barium appeared at both lung bases, more on the right than on the left. At the same time he developed tachycardia, tachypnoea, and hypotension. Since gastric distension had been prevented by aspiration of the stomach contents, and the patient was noticed to cough after drinking, it is thought that the barium reached the lungs during swallowing. Twenty days after operation he began to vomit; the pulse and respiration rates increased, and he died three hours

later. Autopsy showed a perforation of the stomach and 'agonal' aspiration of gastric contents, which had entered the alveoli.

Case 6 (R.I. 31876). A woman aged 63 was moribund, with arteriosclerotic gangrene of the foot. No operation was done. She inhaled barium, mainly into the right lung, on the day before her death (Plate 28, Fig. 4). It is probable that drinks were inhaled.

Case 7 (R.I. 181201). A man aged 69 had gastroenterostomy for carcinoma of the stomach on 7.10.53. Four days after the operation, although alert, he began to inhale barium, and three days later he was dead. One of the radiographs showed the oesophagus full of barium (Plate 28, Fig. 5); so regurgitation may have accounted for some of the inhalation, although vomiting was infrequent. The opacities seen in the lung fields proved at autopsy to be infarcts filled with barium.

Case 8 (R.I. 185422). A man aged 88 had suprapubic cystotomy on 1.1.54 for prostatic obstruction. He was fairly well until 24 hours after the operation, when he began to vomit, and in 10 minutes was dead. This was undoubtedly an example of inhalation of vomit (Plate 29, Fig. 6).

Case 9 (R.I. 16566). A man aged 61 underwent total colectomy on 28.10.53 for ulcerative colitis. A short time after the operation he became very ill with enteritis. Besides intensive fluid and electrolyte therapy, two intra-arterial blood transfusions and two bronchoscopic 'toilets' were necessary. On the day after operation the first of many aspirations of barium occurred (Plate 29, Fig. 7). These mainly affected the base of the right lung, and occurred in spite of intermittent gastric aspiration to prevent vomiting. He eventually made a complete recovery, and a bronchogram 17 months later showed no residual lung damage.

Case 10 (R.I. 18328). A man aged 76 had retropubic prostatectomy on 18.11.53. Two days after the operation pyrexia, tachycardia, and tachypnoea set in. Bronchoscopy showed barium in the bronchi, and this was confirmed by radiography (Plate 29, Fig. 8). He died a few hours later. Since no vomiting occurred, the condition could have been due either to aspiration of feeds or to regurgitated stomach contents.

This investigation showed that barium administered by the mouth entered the lungs of 10 out of 94 patients (10·6 per cent.); but in many of these cases it was not clear whether food or vomit had been inhaled. To clarify this point a further series of patients was investigated.

Second experiment: aspiration of vomit

Method. In a similar series, 51 patients were given barium, this time by tube directly into the stomach. In these patients the appearance of barium in the lungs could only mean that gastric contents had been inhaled. Sufficient barium was introduced down the tube to make the concentration in the stomach approximately one part in five, so that, for every four ounces of fluid given by mouth, one ounce of barium suspension was administered. Daily radiographs of the chest were taken, as in the first series.

Results. Only one patient in this second series inhaled vomit, and this occurred after the barium had been discontinued.

Case 11 (R.I. 192039). A man aged 65 had retropubic prostatectomy on 11.6.54. Five days after the operation he developed a mild stapylococcal

enterocolitis. It was decided to pass a naso-gastric tube to relieve the abdominal distension, but while this was being done, with the patient in the sitting position, he vomited, inhaled, and died instantly. Bronchoscopy showed vomit in the air passages, and this was confirmed macroscopically and microscopically at autopsy.

Analysis of Experimental Results

Since only one instance of inhaled vomit was encountered in the second series of 51 patients, who had barium introduced directly into the stomach, it is probable that most of the patients in the first series who inhaled barium did so during feeding, and not from regurgitation or vomit. In fact, only one patient of the 94 in the first series can be said definitely to have inhaled vomit (Case 8), an incidence in the combined series of two in 145 (1·4 per cent.). Of the remaining nine patients who inhaled barium, four had indwelling naso-gastric tubes, through which the stomach contents were being aspirated one- or two-hourly. In these four cases regurgitation was unlikely, and the barium was probably inhaled from their food. This circumstance, and the results in the second series, make it likely that the remaining five patients also aspirated barium from their food; if so, the incidence of food aspiration was nine in 94 (9·6 per cent.). In five of these nine patients the aspirations were multiple, as judged from the radiographs and from the changes in respiration, pulse-rate, and blood-pressure.

Factors Influencing Aspiration

As might be expected, such aspirations occur most readily in the aged and infirm, in people with dysphagia, and in comatose patients. Nevertheless, young and apparently healthy people are not immune.

Age and health. The average age of the patients in the first series who inhaled barium was 69—11 years older than the average of those who did not (Table I). Most, but not all (seven out of 10), were in feeble health at the time of the inhalation. In the whole of the first series 19 patients died, and of these eight inhaled barium.

State of consciousness; narcotics. More than half of the patients who inhaled barium were receiving hypnotics, but in all except one (Case 2) the doses were small. Five patients were drowsy, at least at times, while the other five were alert during their waking hours.

Type of operation. Operations in both series of patients were representative of the work of a general surgical unit, with a bias towards gastric surgery. So far as could be judged from this relatively small total of cases, no particular type of operation seemed to predispose to aspiration; indeed, two of the five patients who had not been subjected to surgery inhaled barium.

Posture. The usual position of patients in both series was sitting, and in all cases in which barium was aspirated it appeared in the lung bases. In four cases the right base only was affected, while in the remaining six it was seen at both bases, and only in one instance was there more in the left side than in the right.

Of the two patients who aspirated vomit, the first (Case 8) was semi-recumbent for most of the time; the other (Case 11) was sitting up at the time of the accident, and there is little doubt that he would have survived if he had been lying on his side when the gastric tube was passed.

TABLE I

Comparison of Patients who did and did not Inhale Barium Given by Mouth

	Patients with barium in the lungs	*Patients with no barium in the lungs*
Average age (years)	69	58
Number of patients	10	84
Deaths — Number	8	11
Deaths — %	80%	13%
Patients noted to have coughed after drinking — Number	9*	35
Patients noted to have coughed after drinking — %	90%	42%

*The 10th patient, who did not cough, inhaled vomit.

Mechanism of Aspiration of Food

In healthy people aspiration of food into the lungs is usually the result of an incautious inspiration, as in laughing or sneezing while the mouth is full. Such aspiration can seldom occur during normal swallowing, for Ardran and Kemp (1952) studied swallowing in approximately 500 normal people by X-ray cinematography, and in no case did barium get through the glottis. In invalids, and especially in the aged, aspiration of barium into the lungs is not infrequently witnessed on the X-ray screen during examination of the pharynx (Kemp, 1956), and is the result of a derangement of the complex mechanism of deglutition which may be motor, sensory, or structural in origin. Oesophageal obstruction at any level inhibits pharyngeal movements, and predisposes to aspiration pneumonia (Ardran and Kemp, 1956); one such patient (Case 4) is reported above. Foreign bodies are said to lead to disturbance of pharyngeal function (Asherson, 1950); naso-gastric tubes, however, appear not to cause such trouble, for more than half of the 94 patients in Series 1 were intubated, whereas less than half (four out of 10) of those who inhaled barium had been treated in this way. Tilting of the head backwards during feeding, and especially during drinking, increases the chances of aspiration. The act of swallowing, normally initiated by the tongue throwing the food back into the pharynx, may sometimes in recumbent or supine positions be disorganized by fluid flowing by gravity into a pharynx unprepared to receive it. Such lapses of the oropharyngeal sphincter are more likely in invalids, and in those who have had a 'radical' tonsillectomy; the chances of subsequent aspiration are presumably greater in those who wear dentures, because of the diminished sensitivity of their pharyngeal trigger-points (Kemp, 1956). Comparative anatomy provides indirect support for these views, in that animals such as cattle, whose offspring, because the mother remains standing, have to suckle with their heads tilted backwards,

have a well protected, partly intranasal larynx, with a long epiglottis that lies on the soft palate.

Mechanism of Aspiration of Vomit: Mode of Death

The same disorders of function that lead to aspiration of food tend also to lead to aspiration of vomit, because pharyngeal and laryngeal movements are likely to be imperfectly co-ordinated with the ejection of gastric contents from the oesophagus. An explanation for occurrences of this kind where vomit does not appear in the mouth was given by Foville (1869), who supposed that, when the posterior orifices of the nose and mouth are closed, as during a violent effort, regurgitated gastric contents may be thrown back from the closed upper pharynx into the trachea with great force, and in sufficient quantity to cause instantaneous death. The phase of respiration at the moment of vomiting is of theoretical importance. Normally this action is preceded by an inspiration that enables the person subsequently to cough and clear the larynx of gastric contents (Chitty, 1834); if, on the other hand, vomiting occurs during expiration, there may be insufficient reserve air with which to cough, and with the next inevitable inspiration vomit is carried deep into the lungs. It is now generally thought that death in this condition may be sudden, from reflex cardiac inhibition, more or less sudden, from mechanical asphyxia, or delayed as the result of pulmonary oedema.

TABLE II

Clinical Features of Cases in which Aspiration of Food is Believed to have Occurred

	Number of cases
Cough after drinking	9/9
Tachycardia	6/9
Pyrexia	5/9
Hypotension	3/6 in which blood-pressure was recorded
Tachypnoea	3/9

Clinical Diagnosis

Aspirations of the kind described are extremely difficult to diagnose. Bile-staining of the sputum may be the only diagnostic sign in patients who are inhaling gastric contents, but when food is reaching the lungs a history of coughing after drinking may lead to the correct diagnosis. Such coughing was observed in nine of the 10 patients reported above who aspirated barium into their lungs, whereas among the other patients only four out of every 10 coughed after feeding. This occurrence must therefore be regarded as a warning sign that aspiration of food or vomit is likely. The physical findings in the nine patients in the first series who are thought to have inhaled food are given in Table II. As would be expected, tachycardia is common, but tachypnoea is surprisingly rare. Pyrexia occurred in more than half of the cases, and hypotension was noted in half of those in which the blood-pressure was recorded.

Morbid Anatomical Diagnosis

The diagnosis, difficult during life, is only a little less so at autopsy; on the one hand it is possible for vomit to have been aspirated into the lungs, and yet not be visible at autopsy, while on the other hand the presence of gastric contents in the bronchi, or even in the alveoli, cannot be taken as evidence of ante-mortem aspiration (Plate 27, Fig. 1) unless, immediately after death and before the body has been moved, measures have been taken to prevent post-mortem gravitation of gastric contents into the lungs. Furthermore, it may be very difficult even microscopically to differentiate between ante-mortem and post-mortem aspirations, because vital cellular reactions continue in the lungs after clinical death (Gardner, 1956). In spite of these difficulties, and in the absence of precautions to prevent post-mortem 'aspiration', ante-mortem inhalation of vomit may often be strongly suspected by those prepared to recognize it. Macroscopically, suggestive signs are otherwise unexplained diffluent haemorrhagic areas in dependent parts of the lungs, perhaps with interstitial emphysema and other signs of asphyxial death. The microscopic appearances, both in man and animals, are well established (de Robert and Hadengue, 1949; Teabeaut, 1952; Moran, 1955); they vary with the time elapsing before death and the kind of material inhaled, although the appearances of inhaled food and inhaled vomit are often similar. That the typical cellular response may occur in patients dying instantaneously is shown by Case 11 (inhalation of vomit). The alveoli contained debris, with many red cells and macrophages, and a few polymorphs, an appearance that suggested an appreciable interval between aspiration and death.

Prevention

Since aspiration is more likely in recumbency, patients should be allowed to drink only while sitting upright. All bottles and feeding cups that facilitate feeding in recumbency should be abolished. There is little doubt that the standard hospital feeding cup was responsible for some of the cases of aspiration described in this paper. Its design makes it easy for the laryngeal defences to be taken unaware. The shape of the spout enables fluid to be poured into the mouth and down the trachea of a recumbent patient, and the hooded top, by concealing from him both the quantity and orientation of the fluid, ensures that he is taken by surprise. If patients are unable to sit up and drink out of conventional cups, they should drink through a straw or tube; if they cannot do this, they must be treated as though they were unconscious, and fed by tube. The volume of gastric contents should be checked from time to time to detect gastric retention and prevent regurgitation. In some cases tracheotomy is necessary to keep the airways clear, but this does not prevent minor degrees of aspiration. It is astonishing how often gastric chyme emerges from the tracheotomy tube when this operation has been performed for severe head injury. This is no new observation, for Porter (1837) noticed food coming through a

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tracheotomy opening, and Bryant in 1860 told of a surgical friend who, when he first observed this phenomenon, feared that he had injured the oesophagus during the operation.

Where there is a tendency to vomit, a prone or semi-prone position is the only safe one for a comatose or weak patient. The patient in Series 2 who died (Case 11) would have lived if he had been placed in such a position while the gastric tube was being passed. It is a most serious matter that a standard instruction manual (*Pye's Surgical Handicraft*, 1956) should make such lethal recommendations as that local anaesthetics should always be used in the pharynx while passing gastric tubes; that unconscious patients should be held in the sitting position, with a gag in the mouth, while the tube is being passed; and that light intravenous anaesthesia is advisable for the passage of tubes in refractory patients. Premature infants are especially prone to dangerous aspirations; aspiration of gastric contents is effectively prevented, and pulmonary complications reduced, by nursing such children in the knee-elbow position (Wigglesworth, 1956). This procedure is well tolerated, and it is seldom necessary even to put a pad under the abdomen to maintain the position. Lastly, if it is necessary to give concentrated sugar solutions, for example to diabetics in coma or in preparation for operation, or to patients having insulin shock treatment, they should be given intravenously, and not into the stomach whence their subsequent aspiration produces severe pulmonary oedema (Edwards, Morton, Pask, and Wylie, 1956).

Treatment

When the patient is co-operative and can cough, postural drainage and physiotherapy may be sufficient to clear the lungs, but otherwise bronchoscopic aspiration is required. It is true that this is only effective in clearing the larger bronchi, but the coughing and bronchial peristalsis that is induced (di Rienzo, 1949) helps also to clear the smaller tubes. Two further measures have been devised to limit the damage to the lung; the first, used by Bernstein in 1953 in Philadelphia and by Scurr in 1954 in this country (Scurr, 1956), consists of pulmonary lavage with about 200 ml. of saline introduced into the bronchi. This treatment is based on the remarkable tolerance of horses and dogs to water poured down the bronchi (Colin, 1873) (Colin gave 21 litres of water intratracheally to a horse in three and a half hours with no ill effect). Bernstein and his colleagues thought that such treatment, if given soon after the accident, prevented pulmonary oedema. The second method is directed against frothing of the oedema fluid and resulting bronchiolar obstruction by bubbles. Striking relief has been reported after inhalations of alcohol vapour, which destroy the bubbles by reducing surface tension (Luisada, 1950; Luisada, Goldmann, and Weyl, 1952; Weyl, 1955). When death threatens immediately after aspiration, intravenous papaverine in large doses might be tried to combat possible reflex spasm of the pulmonary vessels. Treatment of the late infective complications follows conventional lines.

Discussion

The present investigation has demonstrated aspiration of food or gastric contents into the lungs in about one in every 10 debilitated surgical patients. There is little doubt that medical patients are similarly affected. Indeed, even in healthy people, the sputum after vomiting is often seen to be so intimately mixed with bile that it is certain that some degree of aspiration has occurred. Experiments in animals show that aspiration, especially if solid matter is present, produces atelectasis and predisposes to bronchopneumonia (Mendelson, 1946; Moran, 1955), much in the same way as Robertson and Morle (1951) and Morle and Robertson (1953 *a*, *b*) showed that aspiration of infected mucus in upper respiratory infections was the cause of many cases of so-called atypical pneumonia in man. Although aspiration of food or gastric contents is clearly a common cause of pulmonary complications after operation, it is not the commonest cause, because 61 per cent. of the patients who were fed with barium showed radiographic evidence of atelectasis or pneumonitis, whereas only 10 per cent. aspirated barium in detectable quantities. Lipoid pneumonia is a recognized result, and bronchiectasis a probable late complication, of repeated minor aspirations. It is well known that in oesophageal diseases repeated major aspirations may produce chronic pulmonary infection and fibrosis (Belcher, 1949). On the other hand, it is possible for patients with oesophago-tracheal fistulae to live for many years without trouble (Stutz, 1951). It seems that aspirations, if not often repeated, may produce little permanent damage. For example, bronchography in Cases 1 and 9, 14 months and 17 months respectively after inhalation, showed no residual damage.

From the medico-legal point of view aspiration of vomit is of great importance. At one time nearly every unexplained death in children was attributed to status thymolymphaticus, a condition in which the large thymus of the normal child was thought to be abnormal, while the atrophied thymus of the slowly dying child was accepted as normal (Boyd, 1927, 1932, 1936). More recently there has been a tendency to attribute otherwise unexplained deaths in infants to sudden fulminating respiratory infection (Werne and Garrow, 1947, 1953; Garrow and Werne, 1953 (31 cases); Bowden and French, 1951 (43 cases)). Such cases show a seasonal incidence, and are associated with minor infections, frequently otitis media. It is well known that children with such minor infections are prone to vomit; and an indication that aspiration of vomit may be the true cause of many of these deaths is given by the work of de Robert and Hadengue (1949), who showed that in the majority of such cases milk constituents or vegetable matter can be demonstrated histochemically in the small bronchi, even though the large ones are clear. Aspiration of vomit is often dismissed as an agonal phenomenon. Sometimes this may be so, but more often it is the *coup de grâce* in an ill patient who might otherwise have a chance of survival. This diagnosis may also be made erroneously in an attempt to explain morbid anatomical appearances that in fact have resulted from gravitation of gastric contents into the lungs after death.

I am much indebted to Mr. Elliot Smith and Mr. Moloney, in whose service the present investigation was carried out, to Drs. Kemp and Ardran for their advice and co-operation, to Dr. Robb-Smith for pathological facilities, and to the staffs of the departments concerned. I also wish to thank Mr. Tugwell for the photographs. The present paper includes the substance of a communication read to the Thoracic Society in March 1956.

Summary

1. Barium was added to the food of 94 patients who had undergone major surgery or who were ill for other reasons. It reached the lungs of 10 patients.

2. Out of a further 51 patients who were given barium directly into the stomach, only one inhaled gastric contents.

3. Aspiration of food was estimated to occur in between nine and 10 per cent., and aspiration of vomit in between one and two per cent., of the patients studied.

4. Factors influencing such inhalations are analysed. Infants and invalids should sit up to drink, and should lie down on their sides, or prone, to vomit or to have tubes passed into the stomach.

5. Feeding cups that facilitate drinking in recumbency should be abolished. If patients cannot sit upright to drink, they should drink through a straw or tube; if they cannot do this, they must be fed directly into the stomach.

6. The clinical diagnosis is discussed. Coughing after drinking is a sign that serious aspirations are likely. One-quarter of the patients who were observed so to cough inhaled barium.

7. Suggested lines of treatment are bronchoscopic aspiration, pulmonary lavage with saline, and alcohol inhalations.

8. Gastric contents were shown to gravitate into the lungs of seven out of 10 patients investigated after death. Pathological diagnosis is made difficult by this factor, and by the vital cellular reaction which has been found to occur in the lungs after clinical death in response to the presence of such material.

9. Previous reports of the aspiration of food and vomit into the lungs are reviewed.

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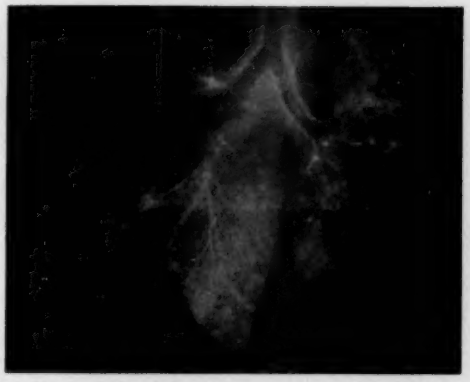


FIG. 1. Radiograph at autopsy of the lungs of a patient into whose stomach barium had been introduced after death. Manipulations during removal of the lungs has squeezed barium into the alveoli

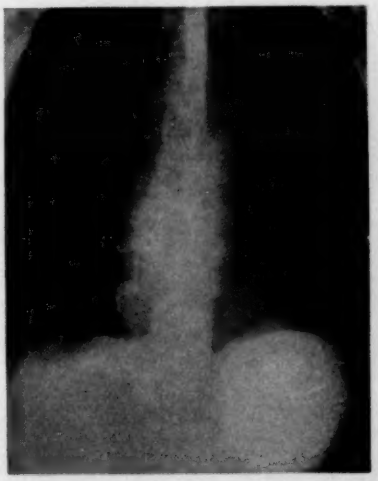
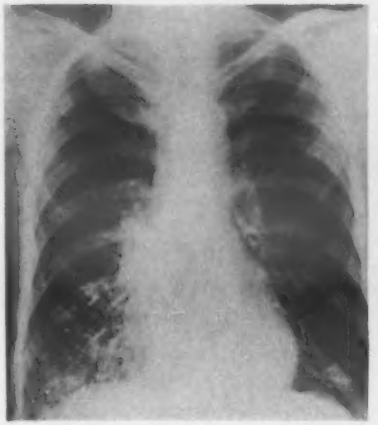


FIG. 2. Case 1. A man aged 47. Barium appeared at the base of the right lung three days after partial gastrectomy for duodenal ulcer. The patient recovered



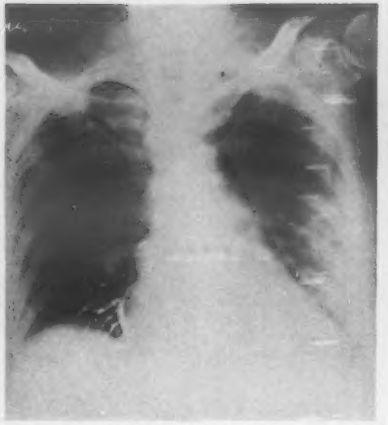
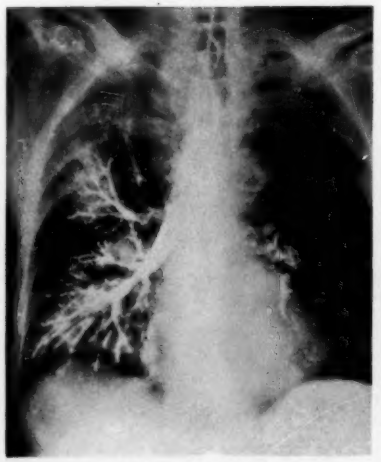


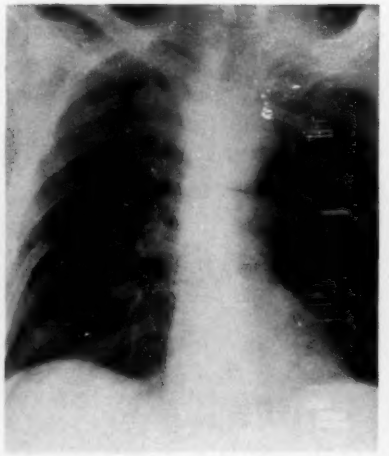
FIG. 3 FIG. 4 FIG. 5

FIG. 3. Case 4. A man aged 73 with carcinoma of the oesophagus; no operation. Barium was aspirated although dysphagia was minimal. The patient died three days later

FIG. 4. Case 6. A woman aged 63 with arteriosclerotic gangrene of the foot; no operation. The patient died on the day after this aspiration

FIG. 5. Case 7. A man aged 69. He began to inhale barium four days after gastroenterostomy for carcinoma of the stomach, and died three days later, a few hours after this radiograph was taken. The opaque round shadows in the lung fields are infarcts filled with barium, presumably as the result of the absence of cilial action in these areas. Note the oesophagus full of barium





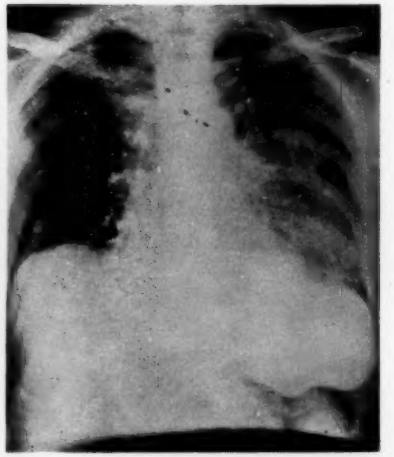


FIG. 6 FIG. 7 FIG. 8

FIG. 6. Case 8. A man aged 88, who had suprapubic cystostomy for prostatic obstruction, and died 24 hours later after suddenly vomiting

FIG. 7. Case 9. A man aged 61. Radiograph taken on the day after total colectomy for ulcerative colitis, showing the first of many aspirations. The patient recovered

FIG. 8. Case 10. A man aged 76, who had retropubic prostatectomy and died two days later, a few hours after aspirating barium into the lungs

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THE TREATMENT OF EOSINOPHILIC LUNG (TROPICAL EOSINOPHILIA) WITH DIETHYLCARBAMAZINE[1]

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THE favourable results obtained with diethylcarbamazine in the treatment of 10 patients suffering from eosinophilic lung (tropical eosinophilia, or pulmonary eosinophilosis) were reported in a preliminary communication (Danaraj, 1956). The present paper reviews the records of 110 patients so treated, and shows that diethylcarbamazine is a safe and effective drug in the treatment of this condition and should replace the organic arsenicals. The therapeutic trial with diethylcarbamazine was conducted in a group of subjects essentially comparable to a group of 150 patients observed by the writer in Singapore and reviewed in 1951. The response to treatment with organic arsenicals in that series, and in a further series of over 500 patients treated since that report, has convinced the writer of the efficacy of organic arsenicals in all cases correctly diagnosed as eosinophilic lung. The use of organic arsenicals, however, is associated with definite risks, so that a search has been made for some form of treatment as effective, but not toxic. It was also felt that, if eosinophilic lung responded to any particular group of drugs, this finding might help in solving the problem of the aetiology of the condition. Groups of patients were treated with various drugs—sulphathiazole, bismuth, penicillin, achromycin, cortisone, piperazine citrate, and diethylcarbamazine—but only diethylcarbamazine was found to be of value. As diethylcarbamazine is known to be effective in the treatment of filariasis, it was important at the outset to exclude this disease, and to select carefully only cases belonging to the clinical entity of eosinophilic lung. In all the patients selected there was no evidence suggestive of past or present filarial infection. The salient features that served to distinguish eosinophilic lung from other respiratory disorders associated with eosinophilia were: (1) a massive eosinophilic leucocytosis (over 3,000 eosinophils per cu. mm.), which was considered essential for the diagnosis; (2) pulmonary shadows in the roentgenograms; and (3) a raised erythrocyte sedimentation rate.

Description of Cases

The study comprised 123 consecutive patients suffering from eosinophilic lung who attended the General Hospital, Singapore, from April 1956; 13 patients, whose attendance was irregular, are excluded from the final series of 110. There was no significant difference in respect of ethnic groups, age, sex,

[1] Received August 6, 1957.

and occupation between this group and the series of 150 cases reported by the writer in 1951; the duration of illness was shorter in the present series, indicating that diagnosis was being made earlier, and with increasing experience minor changes in the radiographs of the chest were more frequently detected. The majority of patients were adult Indians, although Singapore has a predominantly Chinese population (76·5 per cent.) (Tables I and II). There were 101 male and nine female patients. Their occupations were many and varied, but most of the patients came from the lower income groups.

TABLE I

Ethnic Groups

	Patients		*Singapore population (estimated percentage, mid-year 1956)*
Ethnic group	*Number*	*Percentage*	
Indians and Pakistanis:			
Southern 64 Northern 16	80	72·7	7·8
Chinese	17	15·5	76·5
Malaysians	8	7·3	12·2
Eurasians	2	1·8	0·9
Others (including Ceylonese)	3	2·7	2·6
	110	100	100

TABLE II

Age Incidence

Age groups	*Number of cases*	*Percentage*
0 to 9 years	4	3·6
10 to 19 „	16	14·5
20 to 29 „	20	18·2
30 to 39 „	39	35·5
40 to 49 „	18	16·4
50 to 59 „	9	8·2
60 to 69 „	4	3·6
	110	100

The duration of illness when they were first seen was variable, the shortest period being one week, and the longest four years; in the majority of the patients (97) it was under six months (Table III). The initial complaint was cough, which was most frequent and severe at night, occurring in paroxysms of a few minutes and productive of slight mucoid or mucopurulent sputum, which was sometimes streaked with blood; sleep was badly disturbed. A feeling of suffocation and breathlessness was usually present after each bout of coughing, and at times was severe enough to resemble bronchial asthma. The severity of symptoms was considered to be slight (cough only) in nine patients, moderately severe (cough with breathlessness) in 75, severe (bronchial spasm) in 25, and very severe (status asthmaticus) in one patient. There was relative freedom from cough during the day, but the patient felt tired and easily

fatigued. Occasional bouts of low fever, lasting for a few days, were noted in 24 cases. Some patients complained of loss of weight, but no weight records were available. A mild ache in one testicle, lasting for a few days, was present in three patients; this rare feature had been noted previously in a few cases seen in Singapore (see Table IV). No history of allergy was obtainable, except in one patient, who suffered from attacks of urticaria. A family history of bronchial asthma was given by six patients. There was no anaemia, and the general

TABLE III

Duration of Illness

	Number of cases
Under 6 months	97
6 months to 1 year	6
Over 1 year	7
	110

TABLE IV

Symptoms

Complaint	*Number of cases*	*Percentage*
Cough only	9	8·2
Paroxysms of cough with breathlessness	101	91·8
Haemoptysis	7	6·4
Fever	24	21·8
Pain in testis	3	2·7

nutritional state of the patients was good. Abnormal physical signs, which were confined to the chest, were present in 88, and consisted of coarse crepitations and rhonchi heard over the bases of the lungs, together with bronchial spasm in 26 patients. Hepato-splenomegaly and generalized lymphadenopathy were not evident.

In nearly all the patients radiological examination of the chest revealed increased striations, with varying degrees of mottling. The striations, which extended almost to the periphery of the lung fields, were most marked in the middle and lower zones. The mottling consisted of numerous discrete, soft, round shadows with ill-defined margins, varying in size from a pin's head to about 3 mm. in diameter, scattered throughout both lung fields; they were most numerous in the basal and mid-zone areas, lessening in intensity from below upwards, leaving the apices clear. Less frequently a conglomeration of mottled shadows was seen, giving rise to small areas of homogeneous opacities, which were usually found in the lower zone. The X-ray picture of the chest before treatment was considered abnormal in 109 patients, and consisted of:

Increased striations only	11 cases
Increased striations and mottling	43 „
Increased striations, mottling, and pneumonitis	51 „
Very extensive changes	4 „

A uniform technique was used in differential leucocyte counts: thin blood films were stained with Leishman's stain, and at least 200 white cells were

counted from fields forming a battlement arrangement along the edge of the film, after the method of MacGregor and Loh (1941). A persistent eosinophilic leucocytosis (more than 5,000 cells per cu. mm. in 106 patients, and between 5,000 and 3,000 in the remaining four) was present in every case, together with an elevated erythrocyte sedimentation rate (Westergren's method) in the majority (99 patients). This massive eosinophilia was considered a diagnostic feature, and persisted during the preliminary period of observation, which varied from two to four weeks before treatment.

One hundred patients were seen during their first attack; a few were seen during their second (nine cases) or third attacks (one case). These 10 patients had previously been treated by the writer with courses of 'neo-halarsine' (oxophenarsine tartrate) injections and cured, so that a comparison with diethylcarbamazine therapy was available in the same patients in 10 instances.

Parasitological investigations included examinations of (1) two samples of blood (1 ml. in 1 per cent. formalin solution) taken on successive nights for examination for microfilariae, (2) sputum for larvae, and (3) stools for helminth eggs. No microfilariae were detected in any of the 220 specimens of blood examined, nor were any larvae seen in the 110 specimens of sputum. The stools, which were examined by the zinc sulphate flotation technique, gave positive results for hookworm and round-worm eggs in 37 and 22 patients respectively, and for larvae of strongyloides in four others. These findings did not differ significantly from those of a similar group of patients admitted to hospital for other complaints. Lymph-node biopsy was done in three patients in whom a few lymph-nodes were just palpable in the axillae; serial sections of these lymph-nodes did not reveal microfilariae or macrofilariae.

Treatment with Diethylcarbamazine

The dosage of diethylcarbamazine given initially to 46 patients was that generally recommended in the treatment of ascariasis: 4 mg. per kg. body-weight given three times daily for a period of four days. Later, two larger dosages were tried: 6 mg. and 10 mg. per kg. body-weight, given thrice daily for five days, to groups of 57 and seven patients respectively. The average total adult dose for each of the three dosage schedules was 3,200 mg., 6,000 mg., and 10,000 mg. respectively. The drug was given after meals in the form of 50 mg. tablets, the syrup being used for children. Except for 11 patients who exhibited severe bronchial spasm and were treated with antispasmodics as well, the patients were given only diethylcarbamazine.

Period of observation. The patients were observed for two to four weeks before treatment was started, and for periods varying up to 14 months (Table V) from the beginning of diethylcarbamazine therapy, so as to note any recurrence of symptoms or rise in the eosinophil count. During the initial phase of the trial 33 patients were admitted to hospital for the duration of treatment and for a subsequent fortnight; they were then followed up as out-patients. Subsequent patients were observed as out-patients. Careful enquiries regarding symptoms

were made at each visit, and frequent physical examinations were carried out. As was noted with arsenotherapy, a decrease in the eosinophil count was the best indication of effectiveness of the drug. Leucocyte counts were done every alternate day during the period of therapy and for the following fortnight, then weekly for two months, and later at monthly intervals for an average period of

TABLE V

Period of observation after beginning of diethylcarbamazine therapy (days)	*Number of cases*
120–149	22
150–179	18
180–209	29
210–239	16
240–269	8
270–299	7
300–329	4
330–359	4
360–389	1
390–419	1
	110

six months. A roentgenogram of the chest was taken and the erythrocyte sedimentation rate recorded before treatment, and one week and three weeks after completion of treatment. Further estimations of the sedimentation rate were done if it remained high.

Analysis of Results

The criteria of cure adopted in the patients treated with diethylcarbamazine were: (1) amelioration of symptoms; (2) disappearance of physical signs in the chest; (3) a decrease in the number of circulating eosinophils to below 3,000

TABLE VI

Effect of Treatment on Symptoms

Freedom from symptoms by	*Dose per kg. body-weight three times a day*			*Number of cases*
	4 mg.	*6 mg.*	*10 mg.*	
End of 1st week . . .	19	36	4	59
,, 2nd ,, . . .	13	20	3	36
,, 4th ,, . . .	14	1	0	15
Total	46	57	7	110
Toxic manifestations . .	2	4	6	12

Note. Four patients, although free from symptoms, were given second courses of diethylcarbamazine when the eosinophil counts, which had fallen, failed to return to satisfactory levels, but these courses were given after the 30th day.

per cu. mm.; (4) a clearing of the radiological picture of the lung; and (5) a return of the erythrocyte sedimentation to normal. Of these criteria the first three were the most important.

Symptoms. Improvement in symptoms was noted by 107 patients on the second to the fourth day after commencement of treatment, while the drug was

still being taken, and progressed steadily until, by the end of the first week, there was complete relief in 59 cases, and a residual cough only in the remaining 48. Of the latter group, 33 experienced further improvement during the course of the second week, and by the 10th to the 14th day they too were completely free from symptoms; the remaining 15 patients, although considerably improved, suffered from residual cough for a further two weeks, becoming free of

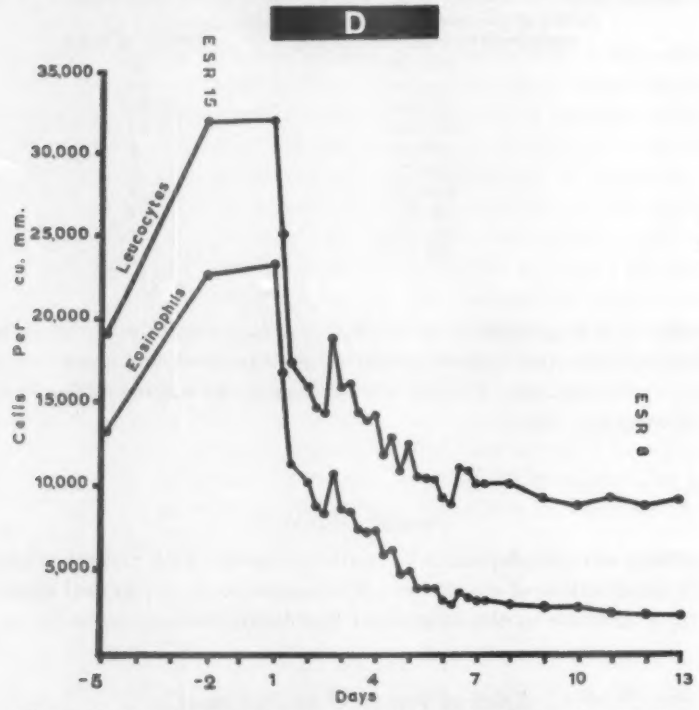

FIG. 1. Six-hourly leucocyte counts illustrating the decrease in cells after the beginning of treatment with diethylcarbamazine (D).
ESR = erythrocyte sedimentation rate (mm. in one hour).

symptoms four weeks after commencement of therapy; 14 of these patients had received the 4 mg./kg. dosage, and one the 6 mg./kg. dosage (Table VI). In two patients symptoms persisted unabated during the period of treatment (6 mg./kg. dosage), but during the second week gradual improvement occurred, and these two also lost their symptoms by the 14th day. With the decrease in the nightly paroxysms of cough and breathlessness, the nights became restful, and sleep was undisturbed—a feature also noted with arsenotherapy. In only one case (4 mg./kg. dosage) was there aggravation of the pulmonary symptoms, accompanied by fever and an increase in the eosinophil count, after the beginning of diethylcarbamazine therapy; this phase lasted for two days before improvement in symptoms occurred, the patient becoming free of symptoms by the 14th day after starting treatment.

Signs. Coincident with symptomatic improvement was a general clearing of abnormal lung signs, and in the majority of patients the lungs were clear by the seventh day after commencement of treatment.

Eosinophil counts. When the leucocyte count was done on the third day of the diethylcarbamazine course, a marked decrease in eosinophils was found in 98 cases; in the remaining 12 patients an increase was noted on the third day, followed by a similar rapid decrease, which was apparent on the fifth

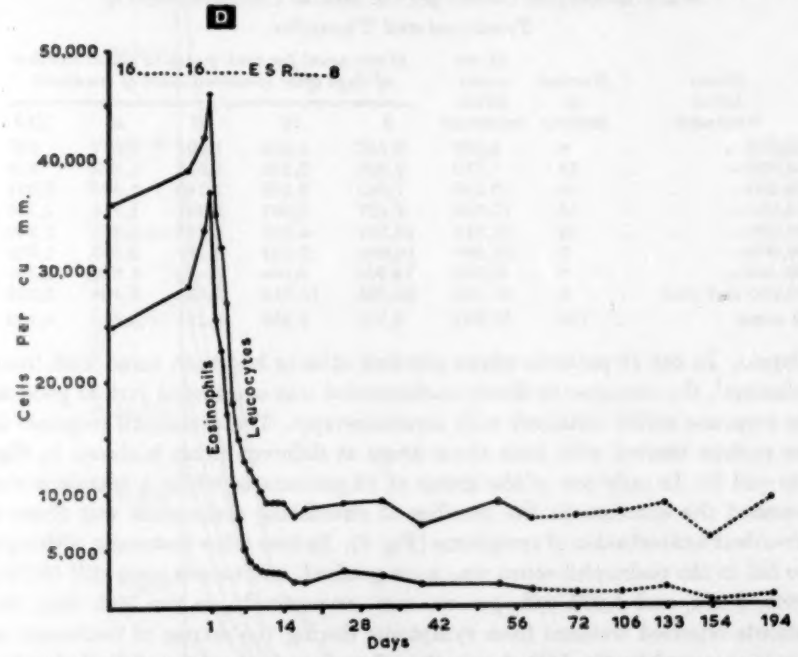

FIG. 2. A typical leucocyte response to treatment with diethylcarbamazine (D). ESR = erythrocyte sedimentation rate (mm. in one hour).

day. Six-hourly leucocyte counts were done in three patients (Fig. 1), and daily counts in 17 others (Fig. 2); the fall in the eosinophil count was observed as early as six hours after the first dose of diethylcarbamazine, and continued steadily and rapidly throughout the first and subsequent days of treatment, reaching levels below 5,000 cells per cu. mm. by the fifth day in some cases, and by the 10th day in the majority of the remainder. The time taken to reach these levels was dependent on the height of the initial counts (Fig. 3); it showed no difference between the three dosage groups, and therefore a separate chart for each group is not presented. In Table VII all the patients who were given one course of treatment have been grouped according to the level of eosinophils at the commencement of treatment, and the mean eosinophil counts for each of these groups are tabulated at five, 10, 20, 30, and 120 days thereafter. After the fifth day a more gradual decrease occurred, and counts below 3,000 and 2,000 cells

per cu. mm. were reached by the 30th day after starting treatment except in six patients; in two of these the eosinophil counts eventually fell to these levels, but four patients required second courses of diethylcarbamazine. Counts below 3,000 eosinophils per cu. mm. were maintained without any increase for the further period of observation, except in three instances to be described below as

TABLE VII

Mean Eosinophil Counts per cu. mm. at Commencement of Treatment and Thereafter

Count before treatment	*Number of persons*	*Mean count before treatment*	*Mean count for each group at stated number of days after commencement of treatment*				
			5	*10*	*20*	*30*	*120*
<5,000	4	4,269	2,742	1,898	1,494	1,077	867
5,000—	31	7,770	4,688	2,765	1,673	1,333	914
10,000—	24	12,540	7,048	3,159	1,740	1,404	1,081
15,000—	18	17,783	8,437	3,987	2,297	1,771	1,176
20,000—	13	22,518	10,524	4,389	2,328	1,708	1,260
25,000—	7	27,360	16,040	6,104	3,166	2,595	1,625
30,000—	5	33,990	14,901	5,094	3,469	2,629	1,540
40,000 and over	4	47,345	25,265	10,658	3,532	2,406	1,399
All cases	106	16,251	8,509	3,856	2,121	1,645	1,132

relapses. In the 10 patients whose previous attacks had been cured with 'neoarsine', the response to diethylcarbamazine was considered just as good as the response earlier obtained with arsenotherapy. The eosinophil response in one patient treated with both these drugs at different times is shown in Fig. 4 (*a* and *b*). In only one of the group of 12 patients in whom a transient rise preceded the decrease in the number of circulating eosinophils was there a coincident exacerbation of symptoms (Fig. 5). In four other instances, although the fall in the eosinophil count was more gradual, and counts were still 10,780, 8,880, 9,600, and 4,032 cells per cu. mm. respectively on the 30th day, the patients reported freedom from symptoms during the course of treatment in three cases, and by the 14th day in the other; a second course of diethylcarbamazine was then given, with a resultant fall in the eosinophil count to less than 3,000 cells per cu. mm. In two further instances, although the patients were free of symptoms by the seventh and 14th day respectively, the eosinophil counts had fallen only to 4,550 and 3,922 cells per cu. mm. on the 30th day; a further decrease to below 3,000 cells per cu. mm. occurred subsequently, although no further treatment was given.

Erythrocyte sedimentation rate. For the purposes of this study a reading of 10 mm. at the end of one hour was regarded as the upper limit of normal. Abnormal readings before treatment were obtained in 99 of the 110 patients, being as high as 20 mm. to 49 mm. in 55 cases, and over 50 mm. in 16 others. The erythrocyte sedimentation rate reverted to normal in 19 patients one week after completion of the diethylcarbamazine course, and in a further 22 patients two weeks later. Although the erythrocyte sedimentation rates in the remaining cases were still abnormal, they had decreased from their original high levels, and over the period of observation continued to decrease, becoming normal in a

further 33 cases; in 25 patients the rates were still above normal at the end of the period of observation.

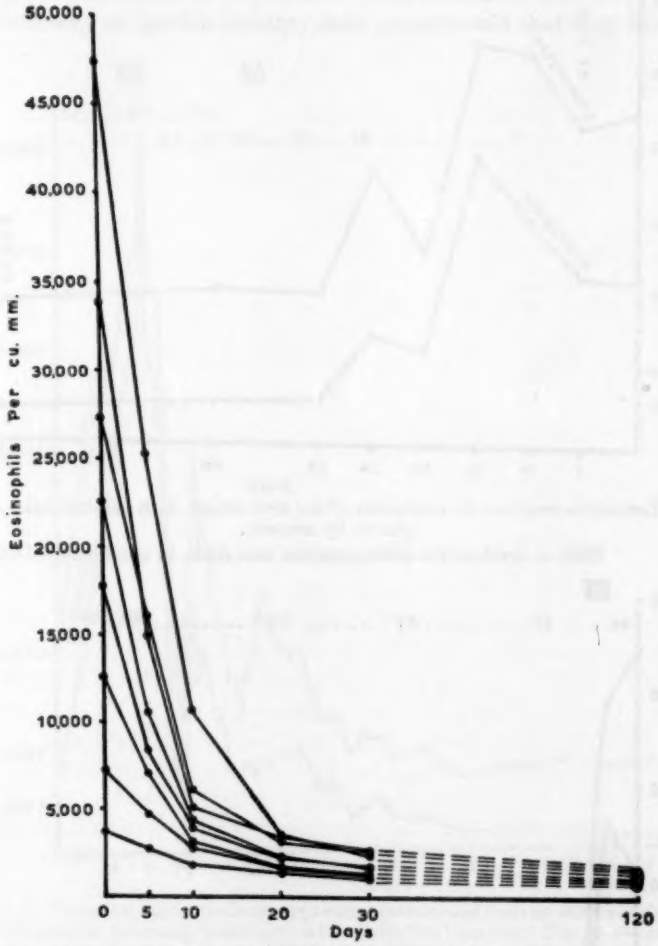

FIG. 3. Mean eosinophil counts in 106 cases at the commencement of treatment and thereafter.

Radiographs. The chest films taken one week after cessation of treatment showed a distinct improvement in all the 109 cases with radiological abnormality, the striations becoming less prominent, with clearing of the pulmonary mottling. Further improvement was noted in the films taken three weeks after cessation of treatment, but minimal residual changes, consisting of no more than slight increase of the markings, were still present, except in two cases, in which the film was considered to be normal. The clearing of the radiological picture was comparable to that obtained with arsenotherapy, with which, although

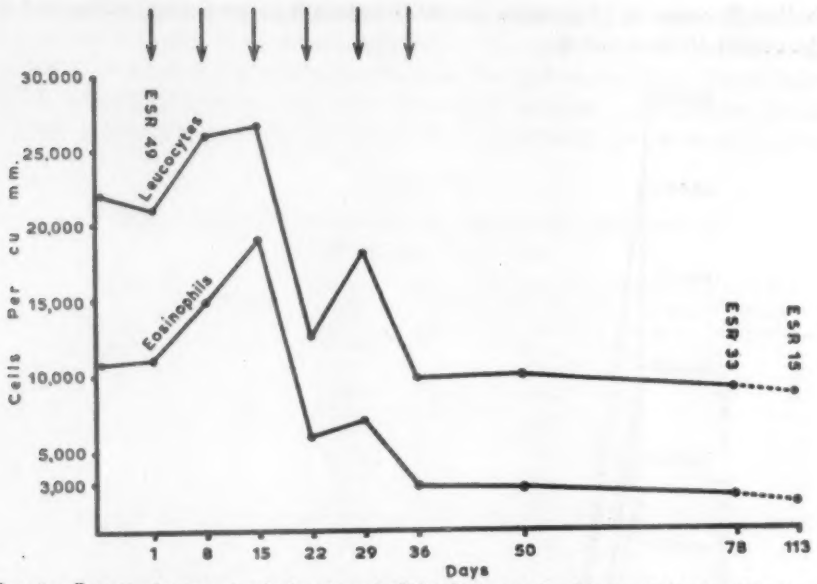

FIG. 4*a*. Leucocyte response to treatment of the first attack with neo-halarsine injections (shown by arrows).

ESR = erythrocyte sedimentation rate (mm. in one hour).

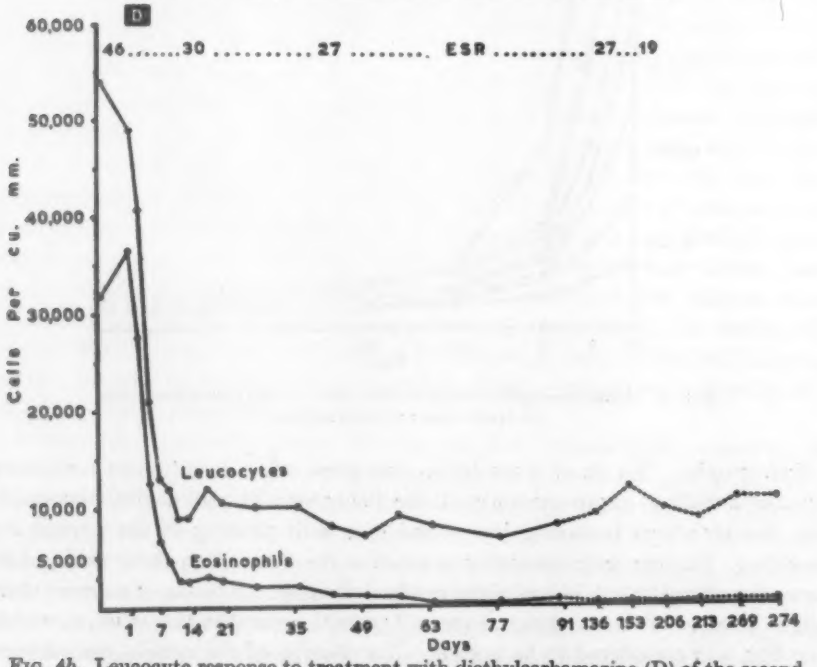

FIG. 4*b*. Leucocyte response to treatment with diethylcarbamazine (D) of the second attack in the case illustrated in Fig. 4*a*.

the pulmonary mottling cleared within a month after completion of treatment, the heavy lung markings took longer to return to normal.

Toxic effects were noted in 12 patients. They were mild, and in six patients were elicited only on specific inquiry; these patients said that they felt a little

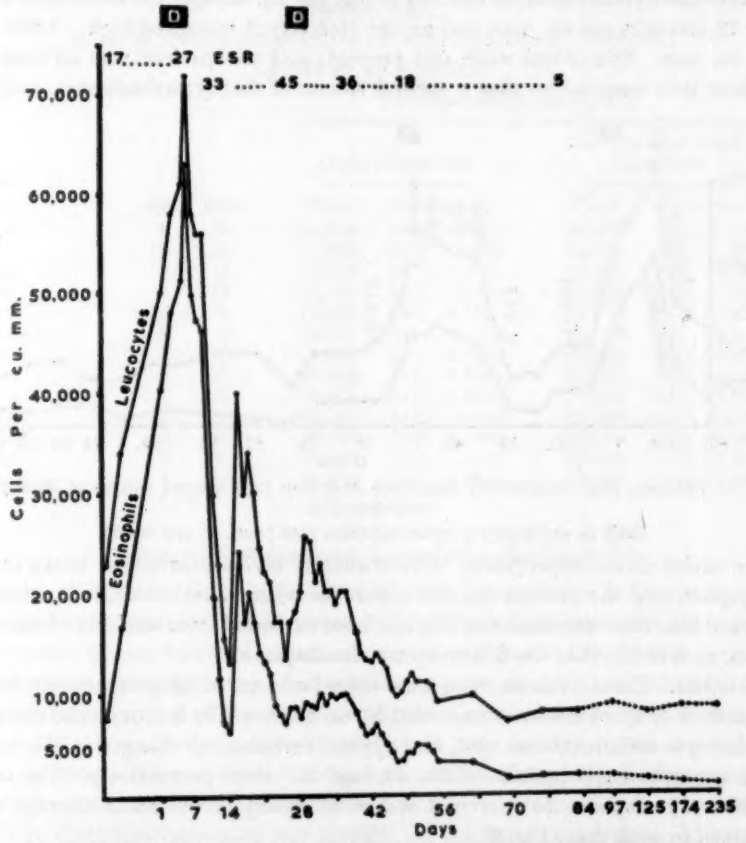

FIG. 5. Transient rise in the leucocyte count (associated with an exacerbation of symptoms) following treatment with diethylcarbamazine (D). A second course of treatment was given when the counts failed to return to satisfactory levels.

ESR = erythrocyte sedimentation rate (mm. in one hour).

giddy, and had vomited once. Two of them belonged to the group of 46 who had been given 4 mg. per kg. body-weight thrice daily for four days, while four were from the group of 57 who had been given the larger dose of 6 mg. per kg. body-weight thrice daily for five days (Table VI). Six of the seven patients who were treated with the third dosage (10 mg. per kg. body-weight per dose thrice daily for five days) complained of their own accord of giddiness and frequent vomiting. In none of the 12 patients with toxic symptoms was it found necessary to reduce the dosage or to cease treatment.

No response. In only one patient was there no symptomatic or eosinophilic response after treatment. He was a male Chinese, who had had cough with breathlessness for six months, and had an eosinophil count of 14,300 cells per cu. mm. (65 per cent. of 22,000 leucocytes). On the fifth day after commencement of diethylcarbamazine therapy (4 mg. per kg. dosage) the eosinophil count was 22,400 cells per cu. mm. and on the 10th day it remained high, 19,600 cells per cu. mm. Symptoms were still present, and the patient was advised admission into hospital so that a second course of diethylcarbamazine could be

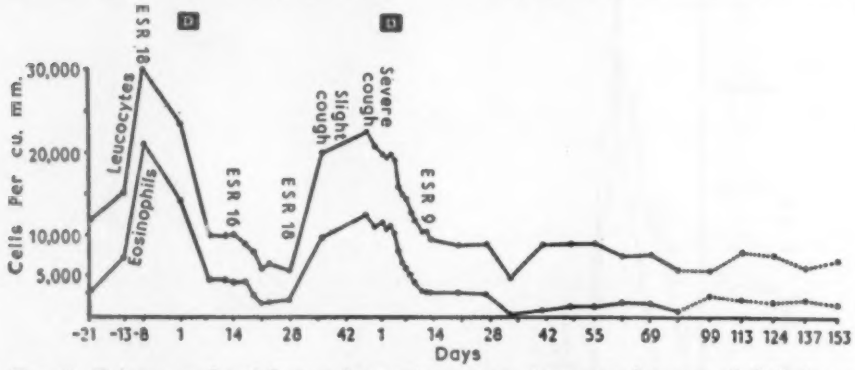

FIG. 6. Relapse, and satisfactory leucocyte response to a second course of diethylcarbamazine (D).

ESR = erythrocyte sedimentation rate (mm. in one hour).

given under direct supervision. Unfortunately civil disturbances broke out in Singapore, and the patient did not report for admission; subsequent attempts to trace him were unsuccessful. He has been excluded from analysis of the final series, as it is felt that the follow-up was inadequate.

Relapses. Three patients, who were considered cured after treatment, had a recurrence of symptoms accompanied by an eosinophilic leucocytosis, elevated erythrocyte sedimentation rate, and typical radiological changes in the lungs, after asymptomatic periods of 28, 46, and 351 days respectively. The same satisfactory response to a second course of diethylcarbamazine therapy was obtained in each case (Fig. 6).

Conclusion. Treatment with diethylcarbamazine resulted in complete cure in all patients, as shown by an amelioration of symptoms, a clearing of the radiological picture, and a decrease in the eosinophils to below 3,000 cells per cu. mm. The erythrocyte sedimentation rate also showed a decrease, though in 25 cases it was still above normal at the end of the period of observation. Although all three dosages of the drug were effective, the symptomatic response was better with the two larger dosages than with 4 mg. per kg. body-weight given three times daily for a period of four days. Of the 15 patients who suffered from a residual cough for three weeks, after initial improvement during the course of therapy, 14 had been treated with the first dosage and the remaining one with the second dosage. Toxic symptoms were more frequent (six out of seven patients) and relatively more severe with the third and largest dosage. The

eosinophil response did not vary with the three different dosage schedules used, a satisfactory decrease in circulating eosinophils occurring with all dosages. The dosage recommended on the basis of this study is 6 mg. per kg. body-weight three times a day for five days.

TABLE VIII

Effect of Diethylcarbamazine on Eosinophilias of Unproved Aetiology in Children

			Leucocyte counts per cu. mm.			
			Before treatment		*30th day after onset of treatment*	
Ethnic group	*Age*	*Sex*	*Total*	*Eosinophils*	*Total*	*Eosinophils*
Indian	6	M	14,000	36% (5,040)	30,000	51% (15,300)
Indian	12	M	12,000	38% (4,560)	14,200	35% (4,970)
Malay	8	M	16,800	30% (5,040)	14,000	25% (3,500)
Malay	2	M	31,000	39% (12,090)	26,200	31% (8,122)
Indian	12	M	16,000	42% (6,720)	20,000	37% (7,400)
Chinese	8	M	29,500	38% (11,210)	13,000	36% (4,680)
Siamese	6	M	9,200	24% (2,208)	11,000	21% (2,310)
Indian	5	F	20,000	33% (6,600)	20,000	33% (6,600)
Indian	8	M	12,000	41% (4,920)	7,800	43% (3,354)
Chinese	2	M	36,000	44% (15,840)	25,000	40% (10,000)
Chinese	6	M	20,400	31% (6,324)	22,000	33% (7,260)
Indian	1	F	30,000	18% (5,400)	13,200	19% (2,508)
Chinese	2	M	18,600	19% (3,534)	18,000	20% (3,600)

Effect of Diethylcarbamazine on other Eosinophilias

Eosinophilia of mild degree (about 1,000 cells per cu. mm.) is frequently seen in tropical countries, and is associated with parasitic infections. Marked eosinophilic leucocytosis, however, is less often seen, and it was this feature, together with pulmonary symptoms and a specific response to arsenicals, that differentiated a large number of cases into a separate clinical entity which is now called eosinophilic lung or tropical eosinophilia. It was decided to see what effect diethylcarbamazine, a non-toxic drug, had on the eosinophilia of other patients, who did not fit into the clinical picture of eosinophilic lung, in order to ascertain whether diethylcarbamazine was specific for the latter condition. A group of 13 children with high eosinophilia, of a degree similar to that seen in patients suffering from eosinophilic lung, was investigated, treated, and followed up in the same way. None of the patients in this group showed clinical or parasitological evidence of filariasis. Some had no complaints, others had vague symptoms of cough, loss of appetite, or abdominal pain, which were not severe and passed off in a few days, often even before treatment was commenced. Radiographs of the chest were normal or showed some increase of the bronchovascular markings. The children were given diethylcarbamazine, in syrup form, in a dosage of 6 mg. per kg. body-weight three times a day for five days; there was no effect on the eosinophilia, which continued for periods of observation of two to 12 months, although the children had no symptoms (Table VIII). One boy, aged six years, has been observed since June 1954, when he had

bronchial asthma and was found to have an eosinophilic leucocytosis of 6,000 cells per cu. mm. (30 per cent. of 20,000 leucocytes). He passed a number of round worms after treatment with santonin, but continued to have asthmatic attacks; he was then given a course of eight injections of neo-halarsine, without any symptomatic or eosinophilic response. His symptoms have recurred almost every month, and the eosinophilia has persisted. Further treatment with

TABLE IX

Effect of Diethylcarbamazine on the Eosinophilia of Patients suffering from Bronchial Asthma

			Leucocyte counts per cu. mm.			
			Before treatment		*30th day after onset of treatment*	
Ethnic group	*Age*	*Sex*	*Total*	*Eosinophils*	*Total*	*Eosinophils*
Indian	32	M	11,000	26% (2,860)	12,600	21% (2,646)
,,	38	M	8,200	16% (1,312)	7,600	13% (988)
,,	25	M	6,800	11% (748)	8,600	8% (688)
,,	30	M	9,200	10% (920)	8,400	8% (672)
,,	28	M	11,800	18% (2,124)	12,600	10% (1,260)
,,	26	M	10,000	17% (1,700)	10,000	15% (1,500)
,,	28	F	10,000	14% (1,400)	12,000	15% (1,800)
,,	44	M	10,200	23% (2,346)	9,000	13% (1,170)
,,	29	M	11,700	20% (2,340)	10,000	16% (1,600)
,,	27	M	9,000	25% (2,250)	9,000	23% (2,070)

piperazine citrate resulted in the passage of more round worms, but without any cessation of the attacks of asthma. In February 1957 he was given a course of diethylcarbamazine, but showed no response. The eosinophil counts were as follows:

Treatment	*Before treatment*	*After treatment*
Neo-halarsine	17,490 per cu. mm.	22,100 per cu. mm.
Diethylcarbamazine . . .	5,040 ,, ,,	15,300 ,, ,,

This lack of response to diethylcarbamazine, and in one patient to organic arsenicals in addition, together with a study of the patients' home conditions, suggests a diagnosis of visceral larva migrans, which can only be confirmed when biopsy or necropsy material becomes available for study. The cases of visceral larva migrans reported so far have not shown any response to treatment with diethylcarbamazine or organic arsenicals (Beaver, Snyder, Carrera, Dent, and Lafferty, 1952; Smith and Beaver, 1955; Dent, Nichols, Beaver, Carrera, and Staggers, 1956). Ten adult Indians, suffering from typical bronchial asthma with mild eosinophilia, were also given diethylcarbamazine, without any response to treatment (Table IX).

Discussion

The use of organic arsenicals in the treatment of asthma with eosinophilia was known in India for many years before the first extensive description of this syndrome by Frimodt-Möller and Barton appeared in 1940, followed by the

report that organic arsenic is a specific therapeutic agent (Weingarten, 1943). The earliest paper that can be traced is by Roy and Bose (1918), who observed the relation between bronchial asthma and hypereosinophilia in their study of 140 patients. The average leucocyte count in 90 cases was 20,000 cells per cu. mm., with an average eosinophil percentage of 48. The highest leucocyte count noted was 58,000 cells per cu. mm., and in one instance the eosinophils formed 89 per cent. of the leucocytes. Roy and Bose treated their patients with courses of subcutaneous or intramuscular injections of 'soamin' (Burroughs Wellcome proprietary name for sodii aminarsonas) with resultant cures in 75 to 80 per cent. of patients. Ghosh, also in 1918, writing on the use of 'soamin' in the treatment of bronchial asthma, stressed the importance of blood examination before treatment, and mentioned that in some of his patients the eosinophilia was as high as 70 per cent. He considered eosinophilia a factor in the selection of patients for this form of treatment, and noted the important fact that patients showing no increase in eosinophils did not improve when treated with 'soamin'. Treu (1944) stated that the 'curative effect of arsenicals on massive eosinophilia' had been known to him since 1933, when he treated his first case successfully with 'arsenotyphoid' injections, and Patel (1945), in a review of 49 cases seen in Bombay, reported that as early as 1930 many practitioners were using neosalvarsan or sulpharsenol freely in cases of asthma, and many had gained a reputation as 'asthma specialists'.

Since the recognition in the tropics of eosinophilic lung (tropical eosinophilia) as a clinical entity nearly two decades ago, numerous papers have appeared attesting to the value of organic arsenicals in its treatment (Simeons, 1943; Jhatakia, 1946; Joseph, 1946; Soysa, 1949; Wilson, 1947; Viswanathan, 1948; Danaraj, 1951). In fact this characteristic response to arsenotherapy clearly demarcates cases of eosinophilic lung from other cases of eosinophilia of different aetiology. Various preparations of organic arsenicals have been used with success—neoarsphenamine, mapharsen (oxophenarsine hydrochloride), and neo-halarsine (oxophenarsine tartrate) intravenously, acetylarsan (diethylamine acetarsol) intramuscularly, and acetarsol or carbarsone orally. It is interesting to note that recently Chaudhuri (1956) used 'soamin' in 10 patients, and obtained a good response in all but one. In view of their potential toxicity, these drugs must be used with some caution, especially in Indians, who seem to show a higher incidence of toxic effects than other races. Such effects were observed in Singapore (with its predominantly Chinese population) when arsenic was the standard treatment for syphilis. Reporting a series of 187 cases of arsenical encephalopathy occurring in members of the Armed Forces in India who were treated for syphilis, Prebble (1946) noted that all except two were Indian patients, giving an incidence of one in 196 Indian patients compared with one in 2,430 British patients; he concluded that Indians were particularly susceptible to this complication, and that individual idiosyncrasy and anaphylaxis were important factors in its causation. Krainer, Black, McGill, and Rao (1947) also reported a high incidence of this reaction among Indian troops undergoing treatment for syphilis.

Of all the toxic manifestations resulting from treatment of eosinophilic lung, arsenical encephalopathy is the one that is especially dreaded, and the writer believes that deaths from this cause have occurred more often than have been reported. Viswanathan (1947) and Singh (1948) each recorded a fatal case of encephalopathy following the use of neoarsphenamine, and Pundit (1949) reported a case with recovery. Two patients with encephalopathy resulting from the use of neoarsphenamine, and one with encephalopathy after the administration of acetylarsan, were admitted under the care of the writer in deep coma, and died shortly thereafter; they had been diagnosed and treated as cases of eosinophilic lung. This complication may also occur with acetarsol: among a series of 138 patients treated with organic arsenicals in Singapore (Danaraj, 1951), encephalopathy developed in an Indian schoolgirl two days after a week's treatment with acetarsol tablets, death ensuing within 24 hours. A further severe case, with recovery, has been reported (Manchanda, 1956) after the use of a similar preparation. Other serious toxic manifestations have been recorded: dermatitis (Danaraj, 1951; Chaudhuri, 1956); melaena (Chand and Chand Gupta, 1947); and agranulocytic angina (Chaudhuri and Chaudhuri, 1945). The total incidence of toxic reactions is probably more frequent than published reports would indicate.

Although the majority of patients improve steadily after commencement of arsenotherapy, some suffer from an exacerbation of pulmonary symptoms, accompanied by a febrile reaction and a rise in the eosinophil count, after the initial treatment, whether given parenterally or orally (Patel, 1945; Jhatakia, 1946). This 'flare-up' or 'Herxheimer reaction' may sometimes be severe enough to resemble acute bronchial asthma or status asthmaticus, requiring the patient's admission to hospital for treatment. Of the present series treated with diethylcarbamazine, only one patient suffered from an exacerbation of symptoms after treatment. A few patients, less than two per cent. according to Viswanathan (1954), do not respond fully to treatment, although some amelioration of symptoms occurs. In the writer's experience only one patient out of a total of over 650 was not cured in spite of two full courses of neohalarsine injections. According to Ball (1950–1), however, cures are obtained in perhaps 50 per cent. of cases only, while in the remainder there is partial relief of symptoms, and some patients are completely resistant to treatment. Return of symptoms and of eosinophil leucocytosis (it is not known whether these were relapses or reinfections) after courses of arsenotherapy occurred in 14 per cent. (Danaraj, 1951) and 20 per cent. (Chaudhuri, 1956) of patients, but they responded satisfactorily to second courses of treatment; as many as three 'relapses' have been noted, each responding satisfactorily to the same treatment (Vaidya, 1943). A further disadvantage of treatment with organic arsenicals is the protracted period of six to eight weeks that is required if the drug is given parenterally, and of 10 days if given orally; the best results are obtained with parenteral treatment, so that this is the usual method. With oral arsenic the clinical response is less prompt, often a second course is required, and toxic reactions appear to be more frequent. The standard treatment finally

adopted by the writer, and used over the last nine years, has been a course of six to eight weekly injections of mapharsen or neo-halarsine given intravenously. Improvement in symptoms occurs after the first or second injection, and by about the fourth injection (fourth week) the patient is usually free of symptoms. Although there was an initial rapid fall in the eosinophil count after the first or second injection, the further decrease was more gradual, and spread out over the six weeks of treatment, until the number of eosinophils fell below 3,000 or 2,000 per cu. mm., but only in a few cases were normal (less than

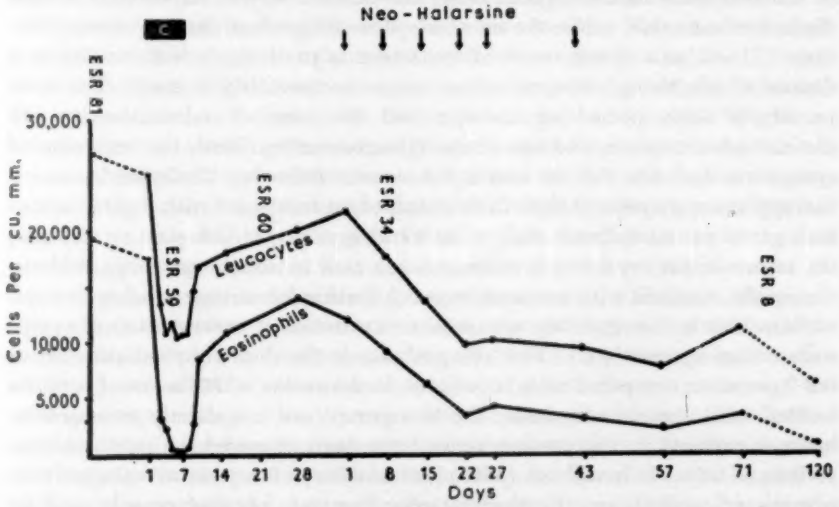

FIG. 7. Leucocyte response to cortisone (C) and subsequent treatment with neo-halarsine injections.

ESR = erythrocyte sedimentation rate (mm. in one hour).

500 cells per cu. mm.) eosinophil counts obtained. The erythrocyte sedimentation rate, re-examined after completion of the course of treatment, also showed a decrease towards normal. The radiological picture taken after this six-week period invariably showed a disappearance of the pulmonary mottling and a decrease in the intensity of the bronchovascular markings; in some cases two months elapsed after completion of treatment before the chest films could be considered normal, while in others some exaggeration of the bronchovascular markings persisted.

Other drugs—sulphapyridine (Lal, 1945), sulphanilamide (Joseph, 1946), bismuth and antimony (D'Abrera, 1946), aureomycin (Rao and Krishnan, 1952; Bannerjie, 1953; Chaudhuri and Chaudhuri, 1953); corticotrophin and cortisone (Sanjivi, Thiruvengadam, and Friedmann, 1955 *a*, *b*; Coutinho, 1956)—have also been tried in the treatment of eosinophilic lung, with either an unsatisfactory or an equivocal response. None have been as consistently effective as the organic arsenicals. In the writer's experience penicillin (used in nine patients), achromycin (in 15), bismuth (in 10), sulphathiazole (in five), cortisone (in 12), and

piperazine citrate (in six patients) did not produce results comparable to those given by arsenic. Only in the patients treated with cortisone was there a constant fall in the eosinophil count towards normal, with a slight amelioration of symptoms and some regression of the abnormal shadows in the pulmonary roentgenograms. Withdrawal of the cortisone, however, resulted in prompt elevation of the eosinophil counts, with a return of symptoms, and cure was only effected after a course of neo-halarsine (Fig. 7).

In comparing the use of diethylcarbamazine with that of organic arsenicals in the treatment of eosinophilic lung, the factor of prime importance is that diethylcarbamazine, unlike the arsenicals, does not produce dangerous complications. Death as a direct result of treatment is particularly unfortunate in a disease which, though incapacitating, causes no mortality in itself. The comparatively short period of therapy and the ease of administration are distinct advantages in the use of diethylcarbamazine. Both the remission of symptoms and the fall in eosinophil counts following diethylcarbamazine therapy are more prompt than those obtained on treatment with organic arsenicals given parenterally or orally; the clearing of the radiological picture and the return of the erythrocyte sedimentation rate to normal are comparable to the results obtained with arsenotherapy. A further advantage in using diethylcarbamazine is the relatively uncommon occurrence of exacerbation of symptoms ('flare-up reaction'). The 'relapse' rate in the diethylcarbamazine series is 2·7 per cent., compared with 14 per cent. in the author's 1951 series of patients treated with organic arsenicals; the two groups are not strictly comparable, because patients in the present series have been observed for much shorter periods of time. It is still not quite clear whether subsequent attacks are true relapses or reinfections. Further attacks, however, respond equally well to treatment with diethylcarbamazine. Lastly, with a relatively safe drug, therapeutic tests can be carried out on patients in whom the diagnosis of eosinophilic lung is in doubt; in the past such patients were subjected to courses of organic arsenicals.

A search of the literature, especially from India (whence most of the papers dealing with this condition have come), has revealed only two references to the use of diethylcarbamazine. The drug was given in a daily dosage of 13 mg. per kg. body-weight, over a period of four days, by Ganatra and Lewis (1955) to 13 patients suffering from tropical eosinophilia, and complete clinical relief, with a return of the eosinophil count to normal, was noted in 11. There were no toxic effects, and they concluded that diethylcarbamazine was an effective drug in the treatment of tropical eosinophilia, the results comparing well with those obtained with carbarsone. Chaudhuri (1956), reviewing 167 cases of the same condition, noted that diethylcarbamazine was fairly effective in 10 out of 12 patients to whom the drug was given, in a daily dosage of 600 to 800 mg., for seven to 10 days. In neither of these reports was it stated whether blood examinations were made to exclude filariasis. An earlier reference to the use of diethylcarbamazine comes, however, from Surinam. Wildervanck, Winckel, and Collier (1953) reported three cases of tropical eosinophilia associated with

histoplasmosis, in which there was no evidence of filariasis; diethylcarbamazine was used successfully in two patients; the third did not react to this drug, but improved after a course of mapharsen.

To avoid confusion between eosinophilic lung and pulmonary filariasis, which was described by Rifkin and Eberhard (1946) and Malhotra (1949), routine blood specimens should be examined for microfilariae before diethylcarbamazine is used. It is necessary to exclude filariasis also because the large doses used in the treatment of eosinophilic lung may give rise to severe systemic reactions in cases of filariasis, for which the recommended dosage is considerably lower.

The aetiology of eosinophilic lung remains obscure. The two important possibilities are that it is an infection and that it is an allergic condition. It may be a combination of both—an allergic reaction to some underlying infection. The current view, and that of the writer, is to regard eosinophilic lung as an infective process resulting from a specific agent which appears to be sensitive to organic arsenicals. In view of the constant clinical and haematological response to diethylcarbamazine, and the absence of this effect in other types of eosinophilia, it is reasonable to presume that this drug also has a direct action against the aetiological agent, rather than a non-specific effect on eosinophile cells. As the drug is known to be effective in cases of ascariasis and filariasis, the possibility of an ascarid or a filarid worm being the aetiological agent should be considered, but piperazine citrate, a drug effective in intestinal ascariasis, has no therapeutic effect in cases of eosinophilic lung, both the symptoms and the eosinophilia persisting. Blood examinations for microfilariae in patients suffering from this disease have been consistently negative. Out of the original group of 150 patients observed by the writer (1951), nocturnal blood films of 61 patients were examined for microfilariae, with negative results in all instances. Again, in the present series of 110 cases, examination of blood samples taken at night failed to reveal the presence of microfilariae. In view of the successful therapeutic results obtained with diethylcarbamazine, an antifilarial drug, Danaraj, da Silva, and Schacher (1957) examined the sera of subsequent sufferers from eosinophilic lung for complement-fixing antibodies, using as antigen a 1 per cent. alcoholic extract of dried powder of *Dirofilaria immitis*, according to the method described by Fairley (1930–1) and Ridley (1956), with slight modifications. Positive reactions in high dilutions of serum were obtained in all of 12 patients suffering from eosinophilic lung, becoming negative after treatment. The filarial complement-fixation test was positive, in relatively low titres, in only some of the sera from cases of filariasis due to *Wuchereria bancrofti* or *W. malayi*, and from dogs infected with *D. immitis*; but in 10 patients with mild eosinophilia and pulmonary symptoms, who were not sufferers from eosinophilic lung, and in 25 healthy controls, the test was negative. All of a further 50 patients suffering from eosinophilic lung have since shown an initially high titre of filarial complement-fixing antibody, with a decline after treatment, but at the date of the present communication the tests had not yet become negative. In none of these fifty patients was there clinical or parasitological evidence of known forms of filariasis.

A human filarid aetiology has been previously advanced for eosinophilic lung on the basis of the histological finding of microfilariae in lymph-nodes of a few patients with hypereosinophilia, lymphadenopathy, and pulmonary symptoms (Meyers and Kouwenaar, 1939; van der Sar and Hartz, 1945; Reisel and Groen, 1951; Bras and Lie, 1951; Friess, Pierrou, and Segalen, 1953; Winter, 1955), but valid objections still exist to this hypothesis. True eosinophilic lung, even in cases of fairly long standing, is not accompanied by any of the classical clinical features of filariasis, such as lymphangitis, adenitis, or elephantiasis, nor have microfilariae been demonstrable in the blood or sputum of such patients (Danaraj, 1951, 1956). Conversely, hypereosinophilia is not a usual feature of filariasis, while pulmonary symptoms, although sometimes recorded, are rare. The clinical pictures of eosinophilic lung and filariasis present reasonably distinct differences. Nevertheless, the aetiological possibility of a filarial infection, not necessarily of a human type, should be considered, in view of the response to treatment with diethylcarbamazine and the finding of sensitivity to filarid proteins as shown by the filarial complement-fixation test in cases of eosinophilic lung.

My thanks are due to Mr. Ong Soon Lim, chief laboratory technician, General Hospital, Singapore, for the blood counts; to Mr. J. F. Schacher, of the Department of Parasitology, University of Malaya, for the examinations of blood, stools, and sputum; to Dr. F. Y. Khoo, Senior Radiologist, General Hospital, Singapore, for the radiological examinations of the chest; and to Mr. Tye Cho Yook, of the Department of Social Medicine and Public Health, University of Malaya, for statistical assistance. I am also indebted to the doctors in Medical Unit I, General Hospital, Singapore, for their help and co-operation in this study.

Summary

Diethylcarbamazine, used in the treatment of 110 cases of eosinophilic lung, was found to be a safe and effective drug. It had no effect on patients suffering from other diseases with eosinophilia. The results obtained compare favourably with those obtained in patients treated with organic arsenicals. It is considered that diethylcarbamazine is a safe and effective drug in the treatment of eosinophilic lung, and should replace organic arsenicals, the use of which has sometimes resulted in encephalopathy and death, an unfortunate result in a disease which, though incapacitating, has no mortality in itself.

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THE RELATIONSHIP BETWEEN THE CLINICAL AND THE HISTOLOGICAL FEATURES OF ACUTE GLOMERULAR NEPHRITIS[1]

Based on a Study of Renal Biopsy Material

By M. S. R. HUTT, J. L. PINNIGER, and H. E. de WARDENER

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With Plates 30 and 31

This paper describes the renal biopsy findings in 15 patients with a clinical diagnosis of acute glomerular nephritis, and compares the clinical features with the extent of the structural changes observed. Patients whose initial clinical features were similar to those of acute glomerular nephritis, but who were proved subsequently to be suffering from some other disease, such as polyarteritis nodosa, are not included.

Methods

Renal biopsy. In accordance with our usual practice, the nature of the procedure was explained to each patient before obtaining permission for the biopsy. A soft-tissue X-ray of the abdomen, or an intravenous pyelogram, was taken a few hours before the biopsy was performed; half an hour before the biopsy pethidine or morphia or methyl pentynol was given. The patient lay in the prone position, and an area of skin in the right renal angle and the tissues down to the kidney were infiltrated with 1 per cent. procaine. The biopsy specimen was obtained with a Silverman needle, and was placed in normal saline for 15 to 30 seconds before being fixed in 10 per cent. formalin. As a routine, serial sections were cut and stained with Ehrlich's haematoxylin and eosin. In selected cases the following stains were also used: Weigert's iron haematoxylin and van Gieson, a modification of Lilley's allochrome, and a trichrome stain (I. W. Whimster and G. P. Goffey, personal communication).

Response of the arterial pressure to a Valsalva manœuvre. This test was performed in order to determine the presence of cardiac failure with greater precision than is possible on purely clinical grounds. The patient was asked to blow a column of mercury to 40 mm. Hg for 10 seconds, while the effect on the systemic blood-pressure was recorded continuously with a capacitance manometer from a needle inserted into the brachial artery (Sharpey-Schafer, 1955).

[1] Received August 14, 1957.

Proteinuria and red cells in the urinary deposit. The presence of protein in the urine was tested by precipitation with salicylsulphonic acid. The rate of red-cell excretion was not measured. Instead, the spun deposit from a random 25 ml. sample of morning urine was examined under the microscope with $\frac{1}{6}$" objective. The excretion of red cells was considered to be raised if there were one or more cells in every field examined.

Creatinine clearance and renal ability to concentrate. The endogenous creatinine clearance was measured over periods of 24 hours; creatinine was estimated by the method of Bonsnes and Taussky (1945). The ability to concentrate was measured after either 36 hours' dehydration or the subcutaneous injection of 5 units of pitressin tannate in oil. The correlation between these two methods has been reported previously (de Wardener, 1956).

Erythrocyte sedimentation rate and serum complement. The erythrocyte sedimentation rate was measured according to Westergren's method (1921), and the serum complement by the method of Dacie (1956).

Clinical Features

Clinically, 14 of the patients (Cases 1 to 14) could be divided into two groups depending on the presence or absence of persistent proteinuria (that is, proteinuria each day for the first few days after admission). Case 15 is considered separately, for, though the patient suffered from a typical attack of acute glomerular nephritis with haematuria, hypertension, and cardiac failure, the renal biopsy was not performed until six weeks later, when he had recovered completely except for the continued presence of proteinuria. All the patients in this series were alive and symptomless one year after their attack of acute glomerular nephritis. A summary of each patient's case history is given in the Appendix.

Patients without persistent proteinuria. There were four patients in this group (Cases 1 to 4). One to four weeks after a respiratory infection they developed transient oedema and cardiac failure; none had a rise in diastolic blood-pressure above 90 mm. Hg. In Cases 1, 2, and 3 protein was never found in the urine, and in Case 4 a trace of protein was found on only two occasions.

Patients with persistent proteinuria. There were 10 patients in this group (Cases 5 to 14). Seven gave a history of a preceding infection, which was followed one to three weeks later by a sudden onset of oedema, a raised jugular venous pressure, hypertension, proteinuria, and haematuria; during recovery there was a rapid and substantial loss of weight. In two (Cases 10 and 13) the same clinical picture was present, except that in Case 10 there was no history of a preceding infection, and in Case 13 there were additional features, including acute arthritis of the knees, a pronounced eosinophilia, and a severe relapse of symptoms a few weeks after a partial recovery. One patient in this group (Case 9) was clinically rather different from the others. Three weeks after a sore throat he developed haematuria and pneumonia concurrently; he had no oedema, rise in jugular venous pressure, or hypertension. It was considered that he might be suffering from 'focal nephritis'.

Histological Features

In Cases 1 to 14 renal biopsies were performed 5 to 17 days after the onset of the first symptom of acute glomerular nephritis; the interval in each patient is illustrated in Fig. 1. On the day the biopsy was performed 13 of these patients had oedema or haematuria, or both. The histological findings were recorded without reference to the clinical state of the patients at the time of biopsy, or to their subsequent progress. The patients were divided into three groups according to the histological lesions found. In the first group the only lesions were

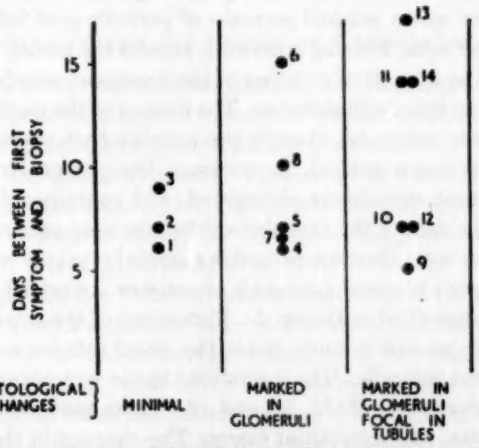

FIG. 1. Number of days between first symptom and the renal biopsy. The histological classification corresponds to the groups A, B, and C in the text; each dot, with the case number, represents a patient.

minimal changes in Bowman's capsule; in the second there were substantial glomerular changes, but no significant lesions in the tubules; and in the third group both tubules and interstitial tissue were involved as well as the glomeruli. The histological lesions in each group are described below; details for each patient are given in the Appendix.

Group A. Cases 1, 2, and 3. The three patients in this group had minimal changes in the cells of Bowman's capsule. The cells were swollen, and had an eosinophilic, granular cytoplasm, with round, usually basal nuclei, forming a layer continuous and identical with that of the cells of the proximal tubules (Plate 30, Fig. 7). This lesion, in some glomeruli, involved the whole capsule, while other glomeruli were only partly involved or were unaffected. Occasionally the free borders of these swollen capsular cells had broken down, so that the capsular space contained a fine granular material like the cytoplasm of the proximal tubules; this material sometimes contained pyknotic nuclei. The presence of this granular material in the capsular space was the only change observed in Case 3.

Group B. Cases 4, 5, 6, 7, and 8. In this group there were striking abnormalities in the glomerular tufts, without any substantial alteration of the tubules

Proteinuria and red cells in the urinary deposit. The presence of protein in the urine was tested by precipitation with salicylsulphonic acid. The rate of red-cell excretion was not measured. Instead, the spun deposit from a random 25 ml. sample of morning urine was examined under the microscope with $\frac{1}{6}$" objective. The excretion of red cells was considered to be raised if there were one or more cells in every field examined.

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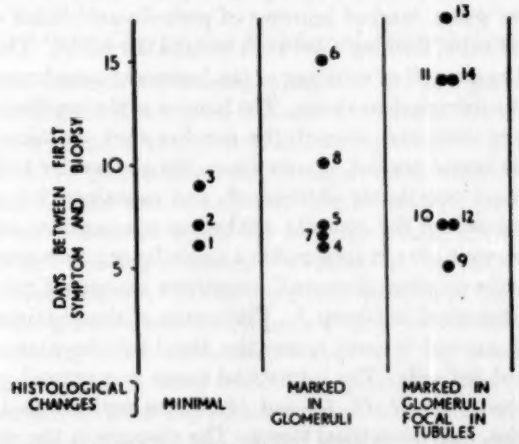

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Group B. Cases 4, 5, 6, 7, and 8. In this group there were striking abnormalities in the glomerular tufts, without any substantial alteration of the tubules

or interstitial tissue. The glomerular changes varied from case to case, from glomerulus to glomerulus, and in any one glomerulus (Plate 30, Fig. 8). All the glomerular tufts were swollen, and capsular spaces narrowed. The tuft swelling was due to an increase of eosinophilic internuclear material, swelling and proliferation of nuclei, and infiltration by polymorphs. In some cases (for example, Case 5; Plate 31, Fig. 9) the nuclear proliferation and polymorph infiltration was conspicuous, leading to distension of the glomeruli; in others (for example, Case 8) there was swelling of the nuclei and an increase of internuclear material, but only slight polymorph infiltration and nuclear proliferation. There was a marked increase of periodic-acid-Schiff staining fibrils in the glomerular tufts, forming a network around the nuclei. They appeared to have developed as a result of splitting of the basement-membrane and irregular extension into the internuclear tissue. The lumens of the capillaries in Cases 4 to 7 were sometimes narrowed, though the number that contained red cells did not appear to be below normal. By contrast, the glomerular tuft capillaries in Case 8 were almost completely obliterated, and contained few red cells. In a few glomeruli the cells of the capsular epithelium were swollen and increased in number, but they were always arranged in a single layer; there were no crescents. The capsular space in some glomeruli sometimes contained granular material similar to that described in Group A. Flattening of the proximal tubular cells was occasionally present in most cases; the distal tubules were normal. A few tubules contained red cells. The interstitial tissue was normal.

Group C. Cases 9, 10, 11, 12, 13, and 14. These patients had lesions in the glomeruli, tubules, and interstitial tissue. The changes in the glomerular tufts were similar to those described in Group B, with certain exceptions in three cases. In Case 12 platelet thrombi and early fibrinoid change were present; in Case 13 there were numerous eosinophils, and in Case 10 there were no polymorphs. The capsular changes were more extensive than those described in Group B, and in some cases there was swelling and proliferation of capsular cells, resulting in crescent formation. The cells of some of the proximal tubules were flattened, as in Group B, but the change was more extensive, and sometimes the lumens were dilated. In contrast to these minor changes there were striking foci of tubular degeneration, which were associated with interstitial oedema and chronic inflammatory-cell infiltration (Plate 31, Fig. 11). The distal tubules were chiefly involved, being dilated and showing degeneration of their epithelium; in some places there was also disruption of the cell wall (Plate 31, Fig 10). At the site of these lesions the lumens of the affected tubules occasionally contained precipitated material. The interstitial tissue surrounding the foci of tubular degeneration was oedematous, and contained numerous inflammatory cells. In Cases 13 and 14, in addition to these focal changes, there was widespread oedema of the interstitial tissue and separation of the tubules. The inflammatory cells were usually histiocytes and lymphocytes, and more rarely plasma cells and eosinophils. Similar collections were occasionally seen round the circumference of a glomerulus. Case 13, in which many eosinophils were present in the glomerular tufts, also showed large numbers in the interstitial

tissue. Red cells were present in the tubules in all cases in this group, particularly in the distal tubules.

Histological appearances during recovery. In Case 15 the renal biopsy was performed four weeks after the onset of recovery, when the only abnormal clinical feature was proteinuria. The sole histological abnormality was a patchy hyperplasia of the nuclei in the glomerular tuft, without polymorph infiltration. There were no significant alterations in the tubules or interstitial tissue.

Relationship between Clinical and Histological Features (Cases 1 to 14)

In general there was a broad measure of agreement, as regards severity, between the clinical and the histological features. Patients with the classical clinical features of acute glomerular nephritis all had proliferative and acute inflammatory changes in the glomerular tufts, whereas those whose only symptoms were oedema and cardiac failure had only minor structural abnormalities in the kidney. A more detailed study of the relationship between individual clinical features and histological changes is described below.

Haematuria and proteinuria. Haematuria occurred only in those patients who had changes in the glomerular tufts (Groups B and C), but its extent bore no relation to the severity of the glomerular lesions or to the presence of tubular changes. Proteinuria did not occur in the three patients (Cases 1 to 3) in Group A, but was persistent in 10 of the patients (Cases 5 to 14) in Groups B and C. One patient in Group B (Case 4), who did not have persistent proteinuria, but in whose urine a trace of protein was found on two occasions, had changes in the glomerular tufts which were similar to those found in patients who were passing much greater quantities of protein. In acute glomerular nephritis, therefore, the presence of proteinuria and haematuria are indications that there are structural lesions in the glomerular tufts, but the extent of the proteinuria and haematuria are no guide to the type of glomerular lesion or to the presence of tubular damage.

Oedema and cardiac failure. There was no relationship between the presence of oedema and cardiac failure, and the histological changes seen in the kidneys. In Cases 1 to 3, with cardiac failure, there were changes only in the capsular epithelium, whereas in Case 9, in which there was no oedema or cardiac failure, glomerular-tuft proliferation and inflammation were present, together with areas of tubular degeneration.

Hypertension. Fig. 2 shows the blood-pressure on the day of admission. The diastolic pressure was below 90 mm. Hg in all three patients in Group A; it was greater than 90 mm. Hg in four of the five patients in Group B, and in five of the six patients in Group C. There appears to be a relationship between the rise in blood-pressure and lesions in the glomerular tufts, though occasionally (Cases 4 and 9) the blood-pressure may remain normal with widespread acute lesions in the glomeruli. There is little indication that the rise in pressure is greater when there are tubular lesions. Early fibrinoid degeneration was seen in an

arteriole in Case 12 (Group C); this patient's blood-pressure on admission was 180/95 mm. Hg.

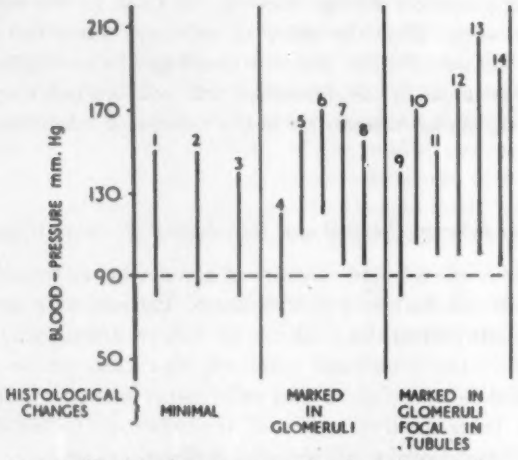

FIG. 2. The blood-pressure on the day of admission. The histological classification corresponds to the groups A, B, and C in the text; each line, with the case number, represents a patient's blood-pressure.

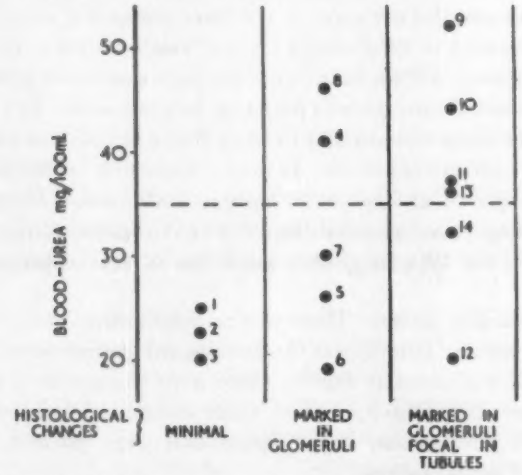

FIG. 3. The blood-urea on the day of admission. The histological classification corresponds to the groups A, B, and C in the text; each dot, with the case number, represents a patient.

Blood-urea. Fig. 3 shows the blood-urea on the day of admission. It was 25 mg. per 100 ml. or lower in all three patients in Group A. Two of the five patients in Group B had blood-urea concentrations above 35 mg. per 100 ml., the higher value being 46 mg. per 100 ml.; in four of the six patients in Group C the blood-urea was more than 35 mg. per 100 ml., the highest level being 52 mg.

per 100 ml. These results suggest that there may be a broad quantitative relationship between the concentration of the blood-urea and the extent of the structural lesions. It is remarkable, however, that seven of the 11 patients with widespread acute proliferative and inflammatory changes in the glomerular tufts should have had blood-urea concentrations below 40 mg. per 100 ml.

Endogenous creatinine clearance. The 24-hour creatinine clearance was measured in only 10 patients. Fig. 4 shows the results obtained a few days after admission. In Group A the clearance was measured in one patient, and was 95 ml. per minute; in Group B it was measured in all five patients, and

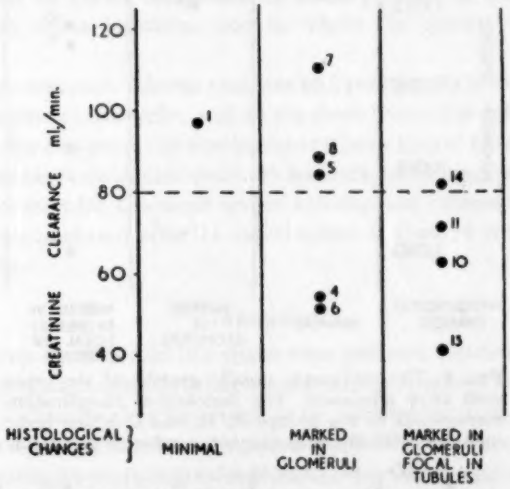

FIG. 4. The creatinine clearance soon after admission. The histological classification corresponds to the groups A, B, and C in the text; each dot, with the case number, represents a patient.

was below 80 ml. per minute in two patients, the lowest clearance being 52 ml. per minute; in Group C it was measured in four patients, in three of whom it was below 80 ml. per minute, the lowest clearance being 42 ml. per minute. These results show that, in general, the structural changes in the glomerular tufts in acute glomerular nephritis are accompanied by a diminished creatinine clearance, and that the creatinine clearance appears to be a more reliable indication of structural abnormality than the concentration of blood-urea. Nevertheless, one patient, who had acute inflammatory and proliferative changes in the glomerular tufts, had a creatinine clearance of 110 ml. per minute six hours before the renal biopsy was performed. There is a suggestion that the creatinine clearance was lowest in those patients who also had definite tubular abnormalities.

Renal ability to concentrate. Fig. 5 shows the maximum urinary concentration obtained a few days after admission. The results are incomplete, for the test was performed in only nine of the 14 patients. In Group A (two patients) the maximum specific gravities were above 1,025; in Group B (three patients)

1,022 or over; in Group C (four patients) 1,021, 1,020, 1,015, and 1,010. The two patients (Cases 13 and 14) with the greatest impairment in concentration had the most severe tubular changes, particularly areas of focal degeneration in

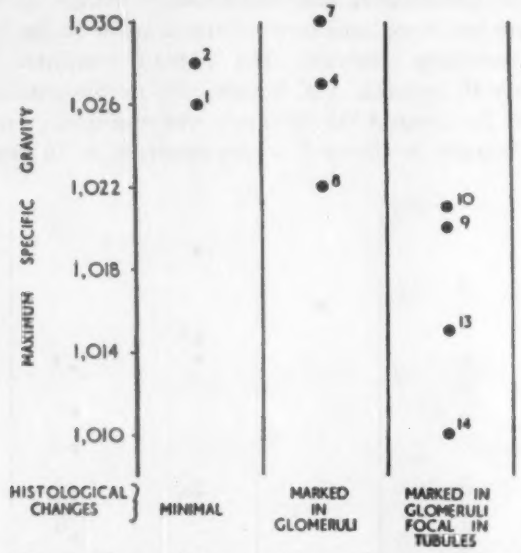

FIG. 5. The maximum specific gravity of the urine soon after admission. The histological classification corresponds to the groups A, B, and C in the text; each dot, with the case number, represents a patient.

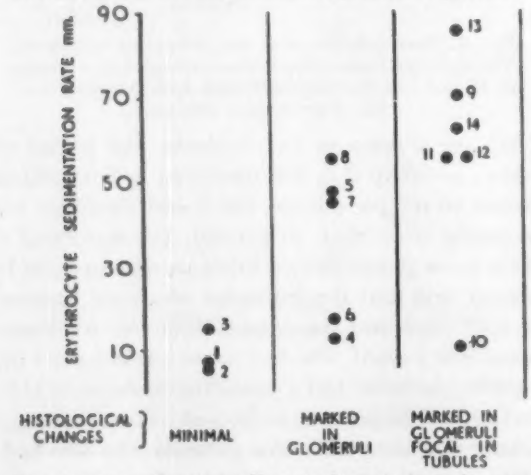

FIG. 6. The erythocyte sedimentation rate (mm. in one hour) on the day of admission.

the distal tubules. In acute glomerular nephritis, therefore, an impairment in the ability to concentrate is an indication of microscopically evident damage in the distal tubules.

Erythrocyte sedimentation rate. Fig. 6 shows the erythrocyte sedimentation rate in all 14 patients on the day of admission. It was 15 mm. in one hour, or lower, in the three patients in Group A; 45 to 55 mm. in three of the five patients in Group B; and 55 to 83 mm. in five of the six patients in Group C. From these results it appears that the rise in the erythrocyte sedimentation rate gives a closer indication of the extent of renal structural damage than any of the other features discussed above. Nevertheless, one patient (Case 10), with changes both in the glomerular tufts and in the tubules, had an erythrocyte sedimentation rate of 12 mm. in one hour; it is probably relevant that she was the only patient in whom the attack of acute glomerular nephritis was not preceded by an acute infection, and in whom the glomeruli contained no polymorphs.

Duration of proteinuria. Eleven patients had proteinuria at the onset; all had changes in the glomerular tufts, and in six there were also definite changes in the tubules. After one year only two patients (Cases 13 and 14) had proteinuria; in both of these cases epithelial crescents had originally been present, and they were the two cases with the most severe tubular and interstitial changes. In Case 13 proteinuria ceased after 14 months, but in Case 14 it was still present after 18 months.

Discussion

The 15 subjects described in this paper were patients consecutively admitted with acute glomerular nephritis; they were unselected, except that children were not included. Clinically they appeared to be a representative group, in which there occurred the usual number of atypical forms of the disease. In general the severity of the attacks was not greater than in other series, and in some respects, for instance duration of proteinuria, it was less; only one patient was dangerously ill (Case 6); the lowest creatinine clearance was 46 ml. per minute; and the highest blood-urea concentration 52 mg. per 100 ml. After one year only two of 12 patients (17 per cent.) still had proteinuria, whereas after the same interval it was still present in 46 per cent. of Addis's cases (1948).

Acute glomerular nephritis without proteinuria or haematuria has often been described (Brod, 1949; Fishberg, 1954; Sharpey-Schafer, 1955). In the present series the three patients without proteinuria showed only 'tubularization' of the cells of Bowman's capsule, that is a reversion of the capsular cells to a type identical with that of the proximal tubules (Plate 30, Fig. 7). We have occasionally seen this change in biopsies from other renal conditions, but not to the same extent; Finckh and Joske (1954) have described similar lesions in renal biopsy material from four cases of diabetes and one of disseminated lupus erythematosus. The lesion can be distinguished from the capsular hyperplasia that precedes crescent formation.

The histological and clinical findings in the remaining patients are discussed in relation to the changes in the glomeruli, and then to the changes in the tubules and interstitial tissue. The series of cases reported here appear to be the first in which renal biopsy has been carried out in the early stages of acute glomerular

nephritis. Brun, Hilden, Iversen, and Raaschou (1956) have given a summary of their findings in 12 patients who were diagnosed clinically as having acute glomerular nephritis; renal biopsies were performed, but the duration of the disease before biopsy is not given. The patients were divided into two groups. The first comprised five fatal cases in patients who histologically showed extensive fibrinoid necrosis of the glomeruli. The second consisted of seven patients, none of whom had 'uraemia or oligoanuria', who showed only minor changes in the glomeruli consisting of slight to moderate hyalinization with varying degrees of endothelial and epithelial proliferation. The condition in the first group is obviously different clinically and pathologically from what is usually described as acute glomerular nephritis; and the renal biopsies in the second group appear, from the histological description, to have been performed at a later stage of the disease than those reported here.

The findings reported in the present paper can be compared, therefore, only with the published accounts of patients who have died within four weeks of the onset. The renal biopsies in our cases show glomerular lesions similar to those described, in cases coming to autopsy, by McGregor (1929), Dunn (1940), Bell (1946), MacManus (1950), and Jones (1953). The classical picture described by these authors is that of a general increase in the size of the glomeruli, which are ischaemic, and show proliferation and swelling of tuft nuclei, an increase of internuclear eosinophilic tissue, and a variable polymorphonuclear infiltration. The majority of these authors have stated that the proliferating nuclei originate only from endothelial cells, but Jones (1953) suggested that epithelial and mesothelial cells also contribute to the increased nuclear content. The absence of red cells in the tufts was thought to be due to obstruction by proliferating endothelial cells. Dunn (1940) and Bell (1946), however, emphasized the observation that in the early stages the capillaries are patent and easily visible. The increase of internuclear material was shown by McGregor (1929) to be associated with a splitting and fragmentation of the basement-membrane, and this finding has been confirmed by other authors (Bell, 1946; Jones, 1953).

The glomerular-tuft changes in our cases were essentially the same as those described above (Plate 31, Fig. 9), but there were a few minor exceptions. The nuclear proliferation and inflammatory-cell infiltration in the glomerular tufts showed a great variability from glomerulus to glomerulus, and even in a single glomerulus (Plate 30, Fig. 8); and the inflammatory-cell infiltration, which usually consisted of neutrophile polymorphs, sometimes contained many eosinophils. The capillary lumens were reduced in size, but in the majority of cases were clearly visible and contained red cells (Plate 30, Fig. 8; Plate 31, Fig. 9), as described by Dunn (1940). In agreement with Allen (1951), we have found it impossible to determine the origin of the majority of the proliferated nuclei in the glomeruli. With the periodic-acid-Schiff stain it was possible to confirm the observation that the internuclear material seen in the glomerular tufts contained a fine network of fibrils, which appeared to be due to splitting and new formation of fibrils from the basement-membrane. Many of our cases showed some swelling or minor proliferation of the cells of Bowman's

capsule. In some cases there were crescents, even when the biopsy was performed as early as seven days after the first symptom; MacManus (1950) found crescents *post mortem* in a patient who died on the third day.

It is surprising that the extensive changes in the glomerular tufts of the patients described here should have been associated with such moderate changes in glomerular filtration rate, that is, in creatinine clearance (Fig. 4). It is probable that the changes in renal blood-flow were even smaller. The renal blood-flow in acute glomerular nephritis has been measured on many occasions, and there is a general agreement that it is either unchanged or reduced only to a small extent, even in patients in whom there is a substantial fall in glomerular filtration rate (Hilden, 1943; Earle, Taggart, and Shannon, 1944; Black, Platt, Rowlands, and Varley, 1948; Hogeman, 1948; Bradley, Bradley, Tyson, Curry, and Blake, 1950; Earle, Farber, and Alexander, 1950). The moderate changes in glomerular filtration rate in our patients are comparable with those reported in patients in whom renal blood-flow measurements have been made.

The best clinical indication that there were structural changes in the glomeruli was the presence of proteinuria and haematuria, though there was no quantitative relationship, as is shown by Case 4. The blood-pressure, creatinine clearance, and blood-urea were also related to structural changes in the glomeruli, though not with such consistency; the poorest guide to the presence of glomerular changes was the blood-urea concentration (Fig. 3).

Most authorities (Dunn, 1940; Bell, 1946; MacManus, 1950; Dible and Davie, 1950; Allen, 1951) have emphasized the fact that the tubular changes in acute glomerular nephritis are usually trivial. In striking contrast, approximately half our cases showed advanced focal degeneration of the tubules (Plate 31, Fig. 10). The lesions affected mainly the distal tubules, but occasionally the proximal tubules also were involved. There was degeneration and necrosis of tubular epithelium, and an associated inflammatory response in the interstitial tissue (Plate 31, Fig. 11). There was no evidence that the tubular lesions were secondary to those in the glomerular tufts. In any case the vascular supply of the tubules is such that glomerular ischaemia is most unlikely to give rise to focal tubular lesions. It is significant that, though the renal blood-flow in acute anuria (Sirota, 1949; Bull, Joekes, and Lowe, 1950; Brun, Crone, Davidsen, Fabricius, Hansen, Lassen, and Munck, 1955) is less than in acute glomerular nephritis, focal tubular necrotic lesions were found less often in renal biopsies from patients with acute anuria (Brun and Munck, 1957) than in our patients with acute glomerular nephritis. This fact suggests that the tubular changes in acute glomerular nephritis are not due to ischaemia, but to a process similar to that which is responsible for the glomerular lesions.

Impairment of the ability to concentrate the urine, which is a reflection of tubular function, has frequently been reported in acute glomerular nephritis (Brod, 1949; Fishberg, 1954). In the present series only two patients (Cases 13 and 14), out of a total of nine in whom a concentration test was performed, had severe impairment of the ability to concentrate (Fig. 5); both had diffuse tubular damage. An erythrocyte sedimentation rate greater than 55 mm. in

one hour was also associated with widespread tubular lesions (Fig. 6). The only exception was Case 10, in which the sedimentation rate was 12 mm. in one hour; this patient was also remarkable in being the only one without a history of a preceding infection. Although the blood-urea concentration tended to be higher, and the creatinine clearance lower, in patients with focal tubular lesions, these tests gave less indication that tubular damage was present than did the ability to concentrate urine or the erythrocyte sedimentation rate.

It was noticeable that red cells were hardly ever present in the capsular spaces, whereas they were often found in the tubules, particularly in patients who had tubular changes. In one patient (Case 12) a necrotic tubular lesion was found adjacent to a capillary, and red cells could be seen extending from the lumen of the capillary into that of the tubule. This finding suggests that tubular damage in some cases of acute glomerular nephritis may contribute to haematuria. It is unlikely that such tubular changes are the main cause of the haematuria, for the amount of blood passed in the urine had no relationship to the presence or extent of the tubular changes; in Case 7, for example, the urine was dark red in colour, but there were no lesions in the tubules.

In one patient in the present series (Case 15) biopsy was performed six weeks after the onset of the disease, when clinical recovery was complete except for persistent proteinuria. Some of the glomeruli were normal; others showed proliferation of tuft nuclei. Only two patients had proteinuria for longer than one year, and in one of these it ceased three months later. Both had glomerular-tuft changes, with capsular crescents, and widespread tubular damage.

We would like to thank Dr. H. K. Goadby and Professor E. P. Sharpey-Schafer for access to their patients, Dr. C. J. Hayter for the records of inter-arterial pressure, Mr. A. E. Clark for his enthusiastic work on the photomicrographs, and Mr. M. G. Ventom for technical help. The expenses of this investigation were defrayed in part by a grant from the Endowment Fund of St. Thomas's Hospital.

APPENDIX

Case Reports

Case 1. A 52-year-old man was admitted to hospital on 28.11.55. Four weeks before admission this patient had a sore throat, followed by a cough and purulent sputum. He had recovered from these symptoms when he developed oedema of the face, ankles, and hands a week before admission. He also began to have headache.

On examination his temperature was 98° F, pulse-rate 48, and respirations 18 per minute. His face was puffy, and there was considerable oedema of the ankles and over the sacrum. The jugular venous pressure was raised 5 cm. above the sternal angle, and the blood-pressure was 150/80. The arterial pressure response to the Valsalva manœuvre was characteristic of heart failure. Many crepitations and a few rhonchi were present at both bases. A chest radiograph showed slight enlargement of the heart. The urine did not contain any protein, and the deposit was normal. After 36 hours' deprivation of fluid the specific gravity of the urine was 1,026. The blood-urea was 25 mg. per 100 ml., and creatinine clearance 97 ml. per minute. The haemoglobin was 13·3 g. per

100 ml., and white blood-cells 7,000 per cu. mm., with 60 per cent. polymorphonuclear neutrophils. The erythrocyte sedimentation rate was 7 mm. in the first hour.

Progress. In the next seven days there was a fall of 14 lb. in weight; the jugular venous pressure fell to normal, the heart-rate rose to 80 per minute, and radiologically the size of the heart returned to normal.

Renal biopsy (No. 5234/55: 28.11.55) was performed six days after the onset of oedema, when it was still present, and the jugular venous pressure was raised (see above). The sections consist of a small piece of cortical tissue with five glomeruli.

Glomeruli. One glomerulus shows 'tubularization' of Bowman's capsular cells, and eosinophilic granular material in the space (Plate 30, Fig. 7). The appearances are similar to those described in more detail in Case 2. The granular material is present in the lumen of three other glomeruli. No polymorphs are present, and there is no appreciable increase in the number of nuclei. Capillaries containing red cells are easily visible.

Tubules and interstitial tissue are normal.

Renal biopsy (No. 5516/55: 14.12.55). The second biopsy was performed when there were no abnormal physical signs. The slides consist of a small piece of cortex containing five glomeruli.

Glomeruli appear slightly bigger than normal, so that the capsular spaces are reduced. Eosinophilic granular material, similar to that seen in the proximal tubules, is present in the capsular spaces of most of the glomeruli. No polymorphs can be identified.

Tubules and interstitial tissue are normal, except that occasional tubules contain red cells.

Summary. This patient developed oedema and cardiac failure, without hypertension, proteinuria, or haematuria, three weeks after a sore throat and a respiratory infection. He recovered within a week of admission. Renal biopsy showed only minor changes in Bowman's capsule and the capsular space.

Case 2. A 41-year-old man was admitted to hospital on 1.10.55. Ten days before admission this patient developed a severe cold, with a cough and yellow sputum; he was in bed for one week. Three days before admission, when he was beginning to get up, he developed oedema of the legs, and the following day his face was oedematous.

On examination his temperature was 99° F, pulse-rate 64, and respirations 20 per minute. His face was markedly oedematous, and there was oedema of the legs up to the knees. The jugular venous pressure was raised 2 cm. above the sternal angle, and the blood-pressure was 150/85. The arterial pressure response to the Valsalva manœuvre was characteristic of heart failure. An electrocardiogram showed no abnormalities. The urine did not contain any protein, and no red cells were seen in the deposit. After 2·5 units of pitressin tannate in oil, given subcutaneously, the specific gravity of the urine was 1,028. The blood-urea was 23 mg. per 100 ml. The haemoglobin was 12·6 g. per 100 ml., and the erythrocyte sedimentation rate 6 mm. in the first hour.

Progress. With rest in bed the patient lost 15 lb. in weight in 15 days and, radiologically, the size of the heart shadow decreased; the haemoglobin increased to 14·8 g. per 100 ml.; the heart-rate increased to an average of 70 to 80 per minute, while the jugular venous pressure, and the arterial pressure response to the Valsalva manœuvre, returned to normal. Five months after admission he was well, and the blood-pressure was 150/85.

Renal biopsy (No. 4285/55: 3.10.55) was performed seven days after the onset of oedema, when it was still evident. The sections consist of a piece of cortico-medullary tissue with six glomeruli.

Glomeruli are of normal size; no nuclear change can be identified in the tufts, and the capillaries appear normal. Internuclear eosinophilic tissue is slightly increased, but there is no alteration in the basement-membrane. Polymorphs are absent. Three glomeruli show well marked 'tubularization' of Bowman's capsule. This change consists of an alteration of the capsular epithelium so that it is identical in appearance with that of the proximal tubules. In some glomeruli there is also a shedding into the capsular space of granular material like that of proximal tubular cytoplasm.

Tubules and interstitial tissue. There is no abnormality apart from the presence of some nuclear debris in the lumens of occasional tubules in the medulla.

Summary. A week after the onset of a severe cold and cough, this patient developed oedema of the legs and face, bradycardia, and cardiac failure; there was no hypertension or proteinuria. He recovered quickly, and has remained well since. Renal biopsy showed 'tubularization' of the cells of Bowman's capsule, with no significant changes in the tufts or tubules.

Case 3. A 54-year-old man was admitted to hospital on 14.12.55. For two weeks before admission this patient suffered from a mild cold followed by a cough. Two days before admission he noticed that his ankles were beginning to swell.

On examination his temperature was 97° F, pulse-rate 50, and respirations 18 per minute. The patient was slightly pale, and his face was puffy. The jugular venous pressure was raised about 2 cm. above the sternal angle, and the blood-pressure was 140/80. The arterial pressure response to the Valsalva manœuvre was characteristic of heart failure. An electrocardiogram showed occasional auricular extrasystoles, but no other abnormalities. The urine did not contain any protein, and there were no red cells or casts in the deposit. The blood-urea was 20 mg. per 100 ml., haemoglobin 11·5 g. per 100 ml., and erythrocyte sedimentation rate 15 mm. in the first hour. A chest radiograph was normal.

Progress. With rest in bed the oedema rapidly disappeared; radiologically, the heart shadow became smaller; after two weeks the haemoglobin was 14·4 g. per 100 ml., the heart-rate averaged 80 per minute, and the arterial pressure response to the Valsalva manœuvre had returned to normal. The patient has remained in good health since.

Renal biopsy (No. 5621/55: 21.12.55) was performed nine days after the onset of oedema. On the day of the biopsy no oedema was evident. The sections consist of a piece of cortical tissue with 11 glomeruli.

Glomeruli are of normal size. There is no apparent increase in nuclei, nor any excess of internuclear eosinophilic material. Polymorphs are absent, and the capillaries appear normal. Slight 'tubularization' and a little eosinophilic granular material are present in a few glomeruli.

Tubules and interstitial tissue are normal.

Summary. After a mild cold the patient developed oedema, bradycardia, and cardiac failure; there was no hypertension or proteinuria. He made a rapid and maintained recovery with rest in bed. Renal biopsy showed no significant abnormalities.

Case 4. A 26-year-old man was admitted to hospital on 25.7.56. Two weeks before admission this patient suffered from a sore throat; he stayed in bed for

five days, and recovered completely. For five days before admission he had had increasing oedema of the face and hands. There were no other symptoms.

On examination his temperature was 98·4° F, pulse-rate 76, and respirations 18 per minute. He looked well. There was oedema of the ankles and over the sacrum. The jugular venous pressure was raised 6 to 8 cm. above the sternal angle, and the blood-pressure was 120/70. The arterial pressure response to the Valsalva manœuvre was characteristic of heart failure. A chest radiograph was normal. The urine usually contained no protein, but a trace was found on two occasions; the deposit did not contain an excess of red or white cells, though an occasional granular cast was found; a culture was sterile. After an injection of 5 units of pitressin tannate in oil the specific gravity of the urine was 1,027. The blood-urea was 41 mg. per 100 ml., and the 24-hour creatinine clearance 53 ml. per minute. The haemoglobin was 12·7 g. per 100 ml., and white blood-cells 5,000 per cu. mm., with 55 per cent. polymorphonuclear neutrophils. The erythrocyte sedimentation rate was 12 mm. in the first hour. The serum complement was 6 units. Culture from a throat swab grew a heavy growth of type 12 β-haemolytic streptococci.

Progress. The jugular venous pressure returned to normal two days after admission, and after a week the patient had lost 6 lb. in weight. On his discharge the haemoglobin was 15·1 g. per 100 ml., and there was a trace of protein in the urine. Seven weeks later there was no proteinuria.

Renal biopsy (No. 3420/56: 26.7.56) was performed six days after the onset of oedema, when it was still evident, and on a day when the early-morning sample of urine showed a trace of protein. The sections consist of cortico-medullary tissue with 10 glomeruli.

Glomeruli are larger than normal, and the capsular spaces are narrowed. All show increased numbers of nuclei, which vary in size and staining quality. The internuclear eosinophilic material is increased, and the periodic-acid-Schiff stain shows that it is associated with a splitting of the basement-membrane. A few neutrophile polymorphs are present, and are usually distributed focally (Plate 30, Fig. 8); in a few places they extend alongside the glomerular arterioles into the periglomerular tissue. The capillary lumens appear reduced in number and size, and contain red cells. Bowman's capsules are normal.

Tubules and interstitial tissue are normal, apart from the presence of red cells in the lumen of one proximal tubule.

Summary. Two weeks after a sore throat this patient developed oedema and cardiac failure; there was no hypertension or haematuria, and only an occasional trace of proteinuria. He recovered rapidly, and seven weeks later there was no protein in the urine. Renal biopsy showed acute inflammatory and proliferative changes in the glomerular tufts. There were no significant tubular abnormalities.

Case 5. A 53-year-old man was admitted to hospital on 21.1.56. Six weeks before admission this patient had a severe sore throat, with a mild fever. He continued to go to work, and recovered. One week before admission he developed dyspnoea, at first on exercise, and then at night; on the night before admission he had three paroxysms of breathlessness. During this week he also developed oedema of the legs and face. For four days his urine had been red, but it had returned to a normal colour on the day before admission. He had had occasional pain in the right loin. His appetite was good.

On examination his temperature was 98° F, pulse-rate 96, and respirations 26 per minute. He looked ill, with a pale, puffy face. There was extensive oedema, extending above the knees and over the sacrum. The jugular venous

pressure was raised 6 to 8 cm. above the sternal angle, and the blood-pressure was 160/110. There were widespread crepitations at both bases. The urine contained protein ++; in the deposit there were only a few red cells and granular casts; a culture was sterile. The blood-urea was 27 mg. per 100 ml., and the 24-hour creatinine clearance 84 ml. per minute. The haemoglobin was 12·9 g. per 100 ml., white blood-cells 9,900 per cu. mm., with 58 per cent. polymorphonuclear neutrophils, and the erythrocyte sedimentation rate 47 mm. in the first hour. A chest radiograph on the morning of 23.1.56 showed extensive consolidation of the right lower zone, probably limited to the right lower lobe, which was partially collapsed; there also appeared to be a small collection of pleural fluid.

Progress. Penicillin was given for seven days from the day of admission. After two days the breathlessness was better, and a week later the patient had lost a total of 19 lb. in weight. On discharge his blood-pressure was 130/80, and there was only a faint trace of protein in the urine. Six months later proteinuria was no longer present.

Renal biopsy (No. 353/56: 23.1.56) was performed seven days after the onset of dyspnoea, two days after frank haematuria had ceased. Oedema, proteinuria, and an increased number of red cells in the urinary deposit, were evident on the day of the biopsy. The sections consist of a piece of cortex with 20 glomeruli.

Glomeruli are larger than normal, and the tufts fill the capsular spaces. There is moderate proliferation of nuclei, which vary in size, shape, and staining quality. Many neutrophile polymorphs are present in each glomerulus (Plate 31, Fig. 9). The capillary lumens contain a reduced number of red cells, and an occasional platelet thrombus. Bowman's capsules are normal.

Tubules and interstitial tissue. Occasional proximal tubules contain red cells.

Summary. Six weeks after a sore throat this patient developed pneumonia, with oedema and cardiac failure, haematuria, and hypertension. He made a rapid recovery, and the urine was free of protein six months later. Renal biopsy showed acute inflammatory and proliferative changes in the glomerular tufts, with no tubular abnormalities.

Case 6. A 28-year-old woman was admitted to hospital on 13.3.56. Three weeks before admission this patient had a sore throat, with shivering and sweating. She was in bed for one week, and after recovery she had a residual cough. For four days before admission she had had increasing dyspnoea. At first the dyspnoea was only evident on exercise, but it then began to wake her up at night, and eventually it was present at all times and prevented her from obtaining any rest. She had put on an unknown amount of weight.

On examination her temperature was 99° F, pulse-rate 100, and respirations 40 per minute. She was in obvious distress with tachypnoea and dyspnoea. The face was puffy, and there was oedema up to the knees. The jugular venous pressure was raised 10 cm. above the sternal angle, and the blood-pressure was 170/120. The apex beat was 9 cm. from the mid-line in the fifth intercostal space. Small bilateral pleural effusions were present. The liver was palpable and tender 2 cm. below the costal margin; there was evidence of fluid in the peritoneal cavity. The urine contained protein ++; on microscopy there was a small increase in red and white cells, and some granular casts; a culture was sterile. The blood-urea was 18 mg. per 100 ml., and the 24-hour creatinine clearance 52 ml. per minute; the haemoglobin was 13·6 g. per 100 ml., the white blood-cells 8,600 per cu. mm., with 70 per cent. polymorphonuclear neutrophils, and the erythrocyte sedimentation rate 17 mm. in one hour. A chest radiograph showed an enlarged heart and bilateral pleural effusions.

Progress. For two days the dyspnoea continued unabated; then there was a diuresis, with a loss of 16 lb. in weight in 10 days. The jugular venous pressure returned to normal, and seven days after admission the blood-pressure was 140/90. Proteinuria was no longer present three months after admission.

Renal biopsy (No. 1307/56: 21.3.56) was performed 15 days after the onset of oedema (eight days after admission). Some oedema, proteinuria, and a slightly increased number of red cells in the urinary deposit were still present on the day the biopsy was performed. The sections consist of a piece of cortex with 20 glomeruli.

Glomeruli are either of normal size, or slightly enlarged where the capsular spaces are reduced. There is some increase in the number of nuclei and in the internuclear eosinophilic material, but the striking feature is the presence of numerous neutrophile polymorphs in all the glomerular tufts. The capillary lumens are reduced in number and size, and contain red cells.

Tubules and interstitial tissue. Apart from slight focal periglomerular oedema, no significant abnormality is present.

Summary. Seventeen days after a sore throat this patient developed severe heart failure with oedema, hypertension, and proteinuria. She recovered rapidly, and three months later the urine was free of protein. Renal biopsy showed acute inflammatory and proliferative changes in the glomerular tufts. There were no significant tubular abnormalities.

Case 7. A 27-year-old man was admitted to hospital on 22.11.56. Five weeks before admission this patient's wife suffered from acute tonsillitis. He himself developed acute tonsillitis three weeks before admission, with shivering and headache. He was treated with a sulphonamide preparation, and was off work for four days. He returned to work, but five days before admission he woke up feeling ill, and since that time his urine had been discoloured, at first dark brown and then purple. During this period he had developed oedema of the ankles, and had put on about 8 lb. in weight; he also noticed that he was passing less urine than normally. There was no dyspnoea or nausea. He had been off work for the five days preceding admission.

On examination his temperature was 99·6° F, pulse-rate 60, and respirations 20 per minute. His face was pale, but not puffy. The jugular venous pressure was raised 3 cm. above the sternal angle, and there was oedema of the ankles and sacrum. There was marked sinus arrhythmia, and multiple extrasystoles. The blood-pressure was 165/95. The urine was the colour of red wine, and contained numerous red cells and granular casts, with protein +++; a culture grew *Bact. coli*. After 5 units of pitressin tannate in oil the specific gravity of the urine was 1,030. The blood-urea was 30 mg. per 100 ml., and the 24-hour creatinine clearance 110 ml. per minute. The haemoglobin was 13·0 g. per 100 ml., the white blood-cells 10,500 per cu. mm., with 71 per cent. polymorphonuclear neutrophils, and the erythrocyte sedimentation rate 45 mm. in one hour. A culture from a throat swab showed a few colonies of type 12 β-haemolytic streptococci. The serum complement was 35 units. A chest radiograph showed a questionable enlargement of the heart.

Progress. Frank haematuria continued for five days, with proteinuria +++. Nevertheless, the jugular venous pressure returned to normal within 24 hours; in the first 10 days the patient lost 14 lb. in weight, and radiologically the size of the heart became smaller. One month after admission the patient's blood-pressure was 140/80, and there was only a trace of protein in the urine. Four months after admission proteinuria had ceased.

Renal biopsy (No. 5368/56: 22.11.56) was performed six days after the onset

of haematuria, when the urine was still dark red in colour. The sections consist of a piece of cortico-medullary junction with seven glomeruli.

Glomeruli vary in size. Some are considerably larger than normal, and show an increased number of pleomorphic and hyperchromatic nuclei. This nuclear increase is often focal. There is an excess of eosinophilic internuclear material, which is shown by the periodic-acid-Schiff stain to be associated with a splitting of the basement-membrane and extensions of its fibrils. A moderate number of neutrophils can be seen in the tufts. Red cells are easily visible in the capillary lumens. Occasionally the cells of Bowman's capsule are a little swollen.

Tubules and interstitial tissue are normal, apart from one focus of degeneration associated with inflammatory-cell infiltration round a sclerotic glomerulus at the edge of the section. Red cells are present in the lumens of two proximal tubules.

Summary. Sixteen days after an attack of acute tonsillitis this patient developed frank haematuria, oliguria, oedema, cardiac failure, and hypertension. During recovery he lost 14 lb. in weight, his blood-pressure returned to normal, and his urine was free of protein after four months. Renal biopsy showed acute inflammatory and proliferative changes in the glomerular tufts, with only minor changes in the tubules.

Case 8. A 35-year-old man was admitted to hospital on 22.5.56. Six weeks before admission this patient, his two children, and his sister all suffered from a sore throat simultaneously. He himself was off work for one month because his doctor thought he looked 'unwell'. Two weeks before admission he returned to work, but three days later he had a relapse of sore throat, more severe than the first time, which continued for seven days. Five days before admission he began to suffer from pain in both loins, and he noticed his urine was becoming dark brown. He felt thirsty, and drank large amounts of water. Three days before admission he developed oedema of the eyes and ankles; he had no dyspnoea, but felt very tired. (During this patient's stay in hospital both his children developed acute glomerular nephritis and had to be admitted to hospital. His sister stated that she felt well, but her doctor reported that she had transient proteinuria.)

On examination his temperature was 99° F, pulse-rate 72, and respirations 20 per minute. His face was oedematous, and there was a healing herpetic lesion on both lips. The tonsils were enlarged and red, and showed occasional pustular follicles. There was oedema of the legs up to the knees; the jugular venous pressure was raised 7 to 8 cm. above the sternal angle, and the blood-pressure was 155/95. A chest radiograph was normal. The urine contained protein ++, and the first sample tested after the patient's admission contained numerous red cells, white cells, and granular casts; but after he had been 48 hours in bed the urine deposit did not appear to be abnormal; a culture was sterile. After 5 units of pitressin tannate in oil, given subcutaneously, the specific gravity of the urine was 1,022. The blood-urea was 46 mg. per 100 ml., and the 24-hour creatinine clearance 87 ml. per minute. The haemoglobin was 15·7 g. per 100 ml., the white blood-cells 11,000 per cu. mm., with 82 per cent. polymorphonuclear neutrophils, and the erythrocyte sedimentation rate 55 mm. in the first hour. A culture from a throat swab grew a heavy growth of type 12 β-haemolytic streptococci.

Progress. The jugular venous pressure returned to normal within three days, and in one week there was a loss of 13 lb. in weight. Proteinuria (+ to + +) continued, and the blood-pressure remained about 140/90. On 10.6.56 the

creatinine clearance was 105 ml. per minute. A month later proteinuria was still +, but seven months after admission it had ceased, and the blood-pressure was 150/80.

Renal biopsy (No. 2319/56: 24.5.56) was performed nine days after the onset of haematuria (five days after the onset of oedema), when the urine deposit was normal but proteinuria was still present. The sections consist of a piece of cortex with nine glomeruli.

Glomeruli vary a little, but the majority are of normal size. The nuclei are swollen and pleomorphic, though not greatly increased in number. There is an excess of internuclear eosinophilic material which, with the periodic acid-Schiff stain, is shown to be associated with a splitting of the basement-membrane and extensions of its fibrils. Only occasional polymorphs can be identified. The capillary lumens are markedly reduced in size, and contain few red cells.

Tubules and interstitial tissue. Some of the proximal tubules are dilated, and are lined by flattened epithelium. The interstitial tissue is normal.

Summary. Six weeks after a sore throat this patient developed oedema, cardiac failure, hypertension, haematuria, and proteinuria. He made a quick recovery, and seven months later his urine was free of protein. Renal biopsy showed slight proliferative changes in the glomerular tufts, with only minor changes in the tubules.

Case 9. A 15-year-old boy was admitted to hospital on 9.3.56. One month before his admission his brother had suffered from pneumonia. The patient himself had had a cough for three months. Three weeks before admission he had a severe sore throat, with shivering and anorexia, for five days. He returned to school on the sixth day, but did not feel well. A week before admission he had dyspnoea on exercise, and his sputum became purulent; a chest radiograph taken six days before admission was normal. He had vomited once a day for three days. On the day of admission he developed macroscopic haematuria and vague abdominal pains. He had then been up and about for the preceding two weeks.

On examination his temperature was 103° F, pulse-rate 110, and respirations 24 per minute. His face was puffy, but there was no pitting oedema of the face, sacrum, or ankles. The jugular venous pressure was normal, and the blood-pressure 140/80. There were localized signs at the left base, with multiple crepitations. The arterial pressure response to the Valsalva manoeuvre was normal. The urine was bright red from the amount of blood it contained; proteinuria was ++; urine culture was sterile; the specific gravity after 5 units of pitressin tannate in oil was 1,020. The blood-urea was 51 mg. and the haemoglobin 12·7 g. per 100 ml., the white blood-cells 15,000 per cu. mm., with 86 per cent. polymorphonuclear neutrophils, and the erythrocyte sedimentation rate 70 mm. in one hour. A chest radiograph showed abnormal shadows at the left base. Culture from a throat swab did not grow β-haemolytic streptococci.

Progress. The patient was treated with penicillin, and made a quick recovery. One month after admission the urine contained only a trace of protein, and six months later proteinuria had ceased.

Renal biopsy (No. 118/56: 14.3.56) was performed five days after the onset of haematuria, when there was still proteinuria and a greatly increased number of red cells in the urinary deposit. The sections consist of a piece of predominantly cortical tissue with 11 glomeruli.

Glomeruli vary in size. The majority are bigger than normal, and show a proliferation of nuclei, which are pleomorphic and sometimes fragmented.

The tufts are infiltrated by neutrophil polymorphs and occasional eosinophils. This infiltration shows some variation from tuft to tuft, and within the lobules of any one glomerulus. The capillary lumens are reduced in number and size, and contain red cells; one is occluded by a platelet thrombus.

Tubules and interstitial tissue. Some of the proximal tubules appear dilated, and occasionally the lumens contain red cells. There is a patchy increase of interstitial tissue, which is associated with degeneration, dilatation, and occasional regeneration in the distal tubules. Red cells are also present in the lumens of these tubules.

Summary. Three weeks after a severe sore throat this patient developed a left lower-lobe pneumonia and frank haematuria, without evidence of oedema, cardiac failure, or hypertension. He recovered rapidly, and the urine was free of protein within six months. Renal biopsy showed acute inflammatory and proliferative changes in the glomerular tufts, with occasional foci of tubular degeneration.

Case 10. A 32-year-old woman was admitted to hospital on 13.9.56. This patient had not felt well for several weeks. She had been depressed and tired, and her back ached. She had not suffered from a sore throat or respiratory infection for at least six months. Seven days before admission she developed oedema of the anterior abdominal wall, which gradually involved the buttocks and the thighs; eventually her fingers, face, and ankles also became swollen. For three days she had been suffering from increasing dyspnoea, at first only on exercise, but on the night before admission she was breathless unless she had four or five pillows, and she occasionally woke up coughing white frothy sputum. For four days she had had severe headache, and thought she had a mild fever. There was no nausea, but her appetite was poor. For one week she had passed much less urine than usual. She was certain she had recently put on about 15 lb. in weight.

On examination her temperature was 99·2° F, pulse-rate 80, and respirations 25 per minute. She had a round, full, oedematous face; her fingers were also obviously oedematous, but there was no detectable oedema of the ankles or sacrum. The jugular venous pressure was raised 2 to 3 cm. above the sternal angle, and her blood-pressure was 170/105. She coughed a great deal, and brought up some white sputum; there were crepitations over both sides of the chest. A chest radiograph showed a slight enlargement of the heart. The urine contained protein +, and there were a moderate number of red cells and casts in the deposit; a culture was sterile. After an injection of 5 units of pitressin tannate in oil the specific gravity was 1,021. The blood-urea was 44 mg. per 100 ml., and the 24-hour creatinine clearance 65 ml. per minute. The haemoglobin was 10·7 g. per 100 ml., the white blood-cells 4,100 per cu. mm., with 71 per cent. polymorphonuclear neutrophils, and the erythrocyte sedimentation rate 10 mm. in the first hour. A culture from a throat swab only grew commensal organisms. The serum complement was 64 units.

Progress. In the two weeks following her admission the patient lost 12 lb. in weight, the jugular venous pressure returned to normal, the blood-pressure fell to 120/60, and the blood-urea to 28 mg. per 100 ml., while the haemoglobin increased to 12·4 g. per 100 ml. A month after admission there was only a trace of protein in the urine, and the deposit was normal. Six months after admission the urine was free of protein.

Renal biopsy (No. 4198/56: 14.9.56) was performed seven days after the onset of oedema (four days after the patient had begun to be breathless). On the day the biopsy was performed oedema was still present, and there was proteinuria

and an increased number of red cells in the urinary deposit. The sections consist of cortical tissue containing 12 glomeruli.

Glomeruli vary in size; the majority are larger than normal, and their capsular spaces are narrowed. The nuclei in the tufts are increased in number, and vary in size and staining quality. There is an associated increase in eosinophilic internuclear material, which with the periodic-acid-Schiff stain is seen to be associated with a splitting of the basement-membrane and extensions of its fibrils. Red cells are present in capillary lumens, which appear slightly reduced in number and size. Only a very occasional polymorph can be identified. There is some thickening of the basement-membrane of Bowman's capsule, with occasional periglomerular fibrosis.

Tubules and interstitial tissue. Small foci of distal tubular degeneration are scattered throughout the section, and are associated with chronic inflammatory cells in the adjoining interstitial tissue. Occasionally the inflammatory cells extend round the glomeruli.

Summary. This patient had no evidence of preceding infection. She was admitted to hospital suffering from oedema, acute cardiac failure, hypertension, proteinuria, and haematuria, and made a quick recovery. Six months later the urine was free of protein. Renal biopsy showed proliferative changes in the glomerular tufts, with some foci of tubular degeneration.

Case 11. A 34-year-old woman was admitted to hospital on 18.10.55. This patient gave a history of 'kidney trouble' following a severe attack of scarlet fever at the age of four years. She had had no symptoms of renal disease since that time. One month before admission she had a sore throat and fever. She stayed in bed for three days, and was treated with a sulphonamide preparation. She gradually felt better, but developed a cough and purulent sputum. Three weeks before admission she had a rash on her buttocks, which responded to an antihistamine drug. She continued to feel unwell, and on the day before admission she vomited six times, and noticed that her face and ankles were swollen.

On examination her temperature was 99° F, pulse-rate 86, and respirations 20 per minute. Her face was puffy, and there was considerable enlargement of the tonsillar glands. The ankles were oedematous, the jugular venous pressure was raised 3 cm. above the sternal angle, and the blood-pressure was 150/100. A chest radiograph was normal. The urine on admission contained only a trace of protein, and no excess of cellular deposit. The blood-urea was 37 mg. per 100 ml., the haemoglobin 13·6 g. per 100 ml., the white blood-cells 9,800 per cu. mm., and the erythrocyte sedimentation rate 55 mm. in one hour.

Progress. During the first two weeks after her admission the patient lost 12 lb. in weight, her blood-pressure fell to 120/75, and the jugular venous pressure returned to normal; but her temperature continued to fluctuate between 99° and 100° F. She gradually excreted increasing quantities of red cells and protein in her urine. On 28.10.55 her urine became purple, and contained many granular casts. The blood-urea concentration remained relatively unchanged, and the 24-hour creatinine clearance at this time was 72 ml. per minute. Two weeks later macroscopic haematuria had disappeared, but proteinuria was still ++. Five months later the urine was free of protein.

Renal biopsy (No. 4770/55: 31.10.55) was performed two weeks after the onset of oedema (four days after the appearance of macroscopic haematuria). On the day of the biopsy there was no oedema, but the urine was dark red. The sections consist of a piece of cortex with 15 glomeruli.

Glomeruli vary in size, and some are larger than normal. There is a patchy increase in the number of nuclei, which vary in shape and tend to be

hyperchromatic. A moderate number of polymorphs are present; they are mostly neutrophils, with occasional eosinophils. In a few places polymorph infiltration extends alongside the glomerular arterioles into the periglomerular tissues; in these areas some of the adjoining tubules show degeneration. There is an increase of eosinophilic internuclear material in the tufts, and some swelling of the cells of Bowman's capsule. Red cells are easily visible in the tuft capillaries.

Tubules and interstitial tissue. Occasionally the proximal tubules are dilated. There are patches of chronic inflammatory-cell infiltration of the interstitial tissue, associated with degeneration of some of the distal tubules. Red cells are present in the lumen of two of the tubules.

Summary. A month after a severe sore throat this patient developed oedema, cardiac failure, and hypertension; there was only a trace of protein in the urine. As she recovered from cardiac failure and lost 12 lb. in weight, she developed gross haematuria. Five months later the urine was free of protein. Renal biopsy showed acute inflammatory and proliferative changes in the glomerular tufts, with degenerative changes in the tubules.

Case 12. A 43-year-old man was admitted to hospital on 12.3.56. Three weeks before admission this patient, his wife, and his two children all suffered from a severe sore throat simultaneously. He was off work for one week, but 10 days before admission he began to feel feverish, and the following day his face was swollen. For eight days before admission he had increasing anorexia, with nausea and vomiting. He stopped going to work six days before admission, when he began to notice swelling of his ankles. For two days he had had oliguria and brown urine.

On examination his temperature was 99° F, pulse-rate 60, and respirations 18 per minute. He looked pale, puffy, and apprehensive. There was considerable oedema of the ankles and over the sacrum. The jugular venous pressure was raised about 5 cm. above the sternal angle, and the blood-pressure was 180/100. The arterial pressure response to the Valsalva manœuvre was characteristic of heart failure. A chest radiograph showed a small pleural effusion at the left base. The urine contained protein +++ and large numbers of red cells; there were also granular casts, and a small number of white cells. The blood-urea was 20 mg. per 100 ml. The haemoglobin was 14·1 g. per 100 ml., the white blood-cells 8,100 per cu. mm., with 84 per cent. polymorphonuclear neutrophils, and the erythrocyte sedimentation rate 55 mm. in the first hour. No pathogens were grown from a throat swab.

Progress. The jugular venous pressure returned to normal within 24 hours of the patient's admission, and within six days he had lost 10 lb. in weight and his blood-pressure had fallen to 110/80. He continued to have protein + in the urine for four months, but nine months after admission proteinuria had ceased.

Renal biopsy (No. 1174/56: 13.3.56) was performed seven days after the onset of oedema (three days after the patient began to notice he was passing 'brown' urine). Oedema, proteinuria, and a greatly increased number of red cells in the urinary deposit, were present on the day the biopsy was performed. The sections consist of a piece of cortex with 20 glomeruli.

Glomeruli vary in size; some are very large, and show complete obliteration of the capsular space. The nuclei are not markedly increased, but vary considerably in size and staining quality. Polymorphs are abundant; the majority are neutrophils, but there are occasional eosinophils; in some glomeruli the distribution of these cells is strikingly focal. Red cells are present in the capillary lumens. Platelet thrombi can be seen in one or two tufts

where the adjacent capillary walls have undergone slight fibrinoid change. Early fibrinoid change is also present in one interlobular arteriole. Some glomeruli contain crescents.

Tubules and interstitial tissue. There is oedema and chronic inflammatory-cell infiltration of the interstitial tissue. The changes are focal, and where they surround distal tubules the latter show severe degeneration and occasionally frank necrosis (Plate 31, Fig. 11). The inflammatory cells consist mainly of histiocytes and lymphocytes, but there are also some neutrophils and eosinophils. There is, in addition, dilatation of proximal and distal tubules, with flattening of their epithelium. The lumens of many distal tubules contain red cells. At one point a necrotic tubular lesion involves a large venous capillary, and there are red cells in both lumens.

Summary. Three weeks after suffering from a sore throat this patient developed oedema, cardiac failure, hypertension, and proteinuria. He made a quick recovery, and the urine was free of protein within nine months. Renal biopsy showed acute inflammatory and proliferative changes in the glomerular tufts, with areas of focal tubular degeneration.

Case 13. A 56-year-old woman was admitted to hospital on 4.11.55. Five weeks before admission this patient suffered from a cold, with a sore throat and violent headache. She was persuaded by her doctor to stay in bed for one week, and she improved, but upon getting up both knees became tender, swollen, firm, and glossy. Macroscopic haematuria appeared two weeks before her admission, and continued thereafter. During this time she also suffered from mild pain in both loins and nocturia. For one week before admission she vomited intermittently, had vague abdominal pains, and felt feverish. It was the nausea which finally compelled her to return to her doctor.

On examination her temperature was 100° F, pulse-rate 90, and respirations 20 per minute. She looked ill and pale. The face was not swollen, and there was no ankle oedema. Both knees were enlarged and tender, and contained much fluid, but there was no erythema of the overlying skin. The jugular venous pressure was raised to 2 to 3 cm. above the sternal angle, and the blood-pressure was 200/100. There were bilateral basal crepitations. A Gregersen test of the stools for occult blood gave a strongly positive result. The urine was dark purple from the amount of blood it contained; there were also numerous white cells and granular casts. Proteinuria was +++, and the urine was sterile on culture. After 36 hours' dehydration the specific gravity of the urine was 1,015. The blood-urea was 36 mg. per 100 ml., and the 24-hour creatinine clearance 41 ml. per minute. The haemoglobin was 12·3 g. per 100 ml., the white blood-cells 9,350 per cu. mm., with 53 per cent. polymorphonuclear neutrophils and 12 per cent. eosinophils, and the erythrocyte sedimentation rate 82 mm. in one hour. A chest radiograph was normal, and radiography of the knees showed bilateral osteoarthritis.

Progress. Three weeks after the patient's admission macroscopic haematuria was no longer present, and proteinuria was +; she had lost 7 lb. in weight, and her jugular venous pressure was normal. The blood-pressure, however, was 190/105, and the erythrocyte sedimentation rate had risen to 101 mm. in one hour; but the patient was worried about her child, and discharged herself from hospital. Three weeks later she returned with nausea, headache, macroscopic haematuria, an arterial pressure of 180/115, and a jugular venous pressure 5 cm. above the sternal angle. She recovered slowly, but for several months she continued to feel unwell from time to time. Three muscle biopsies were performed during the next six months, but no evidence of polyarteritis was found.

Proteinuria continued for about one year, but ceased 15 months after the patient's first admission.

Renal biopsy (No. 4291/55: 9.11.55) was performed 17 days after the onset of haematuria, when it was still evident macroscopically. The sections consist of a piece of predominantly cortical tissue with 12 glomeruli.

Glomeruli vary in size, but only a few are larger than normal. Some glomeruli show a small increase in the number of nuclei, which vary in shape but stain uniformly. There is a marked increase in eosinophilic internuclear material. Polymorphs are numerous, and are often focally distributed; a high proportion are eosinophils. Capillary lumens are reduced in number and size, and contain red cells. One glomerulus contains an epithelial crescent.

Tubules and interstitial tissue. There is patchy oedema and chronic inflammatory-cell infiltration of the interstitial tissue, including a number of eosinophils. The inflammatory foci are usually in areas where distal tubules are degenerating, and in a few places the tubules are necrotic (Plate 31, Fig. 10). In addition, some of the proximal and distal tubules are dilated, and are lined by flattened epithelium. Red cells are present in the lumens of some distal tubules.

Summary. Three weeks after a severe sore throat this patient developed frank haematuria, cardiac failure, and hypertension; she also had swollen knees and eosinophilia. She made a slow recovery, interrupted by a return of all her symptoms. Proteinuria continued for one year, but ceased after 15 months. Renal biopsy showed acute inflammatory and some proliferative changes in the glomerular tufts. There was chronic inflammatory-cell infiltration of the interstitial tissue, associated with distal tubular degeneration and necrosis.

Case 14. A 29-year-old man was admitted to hospital on 27.3.56. Three weeks before admission this patient developed a severe sore throat; he was in bed for two days, and off work for five. Two weeks before admission his urine became dark brown, and he began to feel unwell. He continued to go to work, and gradually began to feel better, though he continued to have a purulent nasal discharge, backache, and anorexia. Four days before admission his face became puffy, and he noticed swelling of the ankles; at this time the urine was a normal colour. On the day of admission the patient still felt a little unwell, but considered that he was recovering. His doctor sent him to hospital on account of proteinuria.

On examination his temperature was 100° F, pulse-rate 80, and respirations 18 per minute. His face was puffy, and there was bilateral enlargement of the tonsillar glands, though they were not tender. There was oedema of the ankles, the jugular venous pressure was raised 3 to 4 cm. above the sternal angle, and the blood-pressure was 190/95. The arterial pressure response to the Valsalva manœuvre was characteristic of heart failure. The urine contained protein +++, and there were many red cells, white cells, and granular casts in the urinary deposit; culture was sterile. After subcutaneous injection of 5 units of pitressin tannate in oil the specific gravity did not rise above 1,010. The blood-urea was 33 mg. per 100 ml., and the 24-hour creatinine clearance 81 ml. per minute. The haemoglobin was 12·6 g. per 100 ml., the white blood-cells 7,500 per cu. mm., with 67 per cent. polymorphonuclear neutrophils, and the erythrocyte sedimentation rate 62 mm. in one hour. A chest radiograph was normal (but see below).

Progress. During the next two weeks the patient lost 5 lb. in weight, the oedema disappeared, and the jugular venous pressure returned to normal; another chest radiograph showed that the heart had become smaller. The

haemoglobin increased to 13·6 g. per 100 ml. Since the patient's discharge proteinuria (+) has continued, and was still present 15 months after his admission; his blood-pressure at this time was 160/70.

Renal biopsy (No. 1425/56: 28.3.56) was performed two weeks after the onset of haematuria (five days after the onset of oedema). On the day of the biopsy oedema was still present, there was proteinuria, and a greatly increased number of red cells were present in the urinary deposit. The sections consist of an undistorted piece of cortex with seven glomeruli.

Glomeruli vary in size; some are very large, and fill the capsular space. There is a variable amount of nuclear proliferation, which is strikingly focal in some tufts. The nuclei vary in shape and staining quality, and are associated with an increase of internuclear eosinophilic material, which with the periodic-acid-Schiff stain is seen to be due, in part, to a splitting of the basement-membrane and extensions of its fibrils. Neutrophile polymorphs are diffusely distributed in the tufts. Red cells are present in some capillary lumens, which appear slightly reduced in number and size. Crescents are present in two glomeruli. There is some chronic inflammatory-cell infiltration round the glomeruli.

Tubules and interstitial tissue. There is widespread patchy oedema and chronic inflammatory-cell infiltration in the interstitial tissue; the inflammatory cells include lymphocytes, plasma cells, and some eosinophils. In these oedematous areas there is usually considerable tubular degeneration, involving both the proximal and distal tubules, some of which appear to have disintegrated. In addition, the tubules in the non-oedematous areas are dilated and lined by flattened epithelium.

Summary. This patient developed haematuria, followed by oedema, cardiac failure, and hypertension, two to three weeks after suffering from a severe sore throat. He made a quick recovery, but still had proteinuria 18 months later. Renal biopsy showed acute inflammatory and proliferative changes in the glomerular tufts, with crescent formation. The tubules showed degenerative changes, associated with chronic inflammatory cells in the interstitial tissue.

Case 15. A 35-year-old man was admitted to hospital on 29.3.56. Five weeks before admission this patient had a severe sore throat; he remained at home for three days, and then returned to work for one week. Three weeks before admission, however, he developed oedema of the ankles, knees, hands, and face, and had great difficulty in putting on his shoes. He then developed dyspnoea on effort, and had to stop work; the dyspnoea increased, and eventually was present even at rest. At this time his urine became brown, and he had oliguria; his doctor reported that his jugular venous pressure was raised, and that there was macroscopic haematuria. He stayed in bed for three weeks, and gradually recovered. On the day of admission he had no dyspnoea, his urine was a normal colour and, whereas he had had severe anorexia, he was now eating normally.

On examination his temperature was 98·4° F, pulse-rate 80, and respirations 18 per minute. There was no oedema, and the jugular venous pressure was normal. The blood-pressure was 150/100. A chest radiograph was normal. The urine contained protein ++, with a moderate number of red cells in the deposit; culture showed a few colonies of *Bact. coli*. The blood-urea was 24 mg. per 100 ml., and the 24-hour creatinine clearance 114 ml. per minute. The haemoglobin was 14·8 g. per 100 ml.

Progress. During the next month the patient put on 5 lb. in weight, and the proteinuria and red-cell excretion diminished. Four months later there was still

a faint trace of protein in the urine, and the blood-pressure was 140/70. Eight months after admission there was no protein in the urine.

Renal biopsy (No. 1780/56: 19.4.56) was performed six weeks after the onset of oedema and haematuria (about four weeks after the onset of recovery); at this time the urine contained a trace of protein, and the blood-pressure was 140/95. The sections consist of slightly distorted cortico-medullary tissue with 10 glomeruli.

Glomeruli vary a little in size, but none is very large. The number of nuclei is increased in some glomeruli. The nuclei vary in size and shape, and show a tendency to be hyperchromatic. There is a slight increase of internuclear eosinophilic material in the tufts, and a patchy increase of periodic-acid-Schiff staining fibrils. Only a very occasional polymorph is present in the tufts, and the capillaries appear normal. Granular material is present in some capsular spaces.

Tubules and interstitial tissue. Occasional proximal tubules are dilated.

Summary. This patient suffered from oedema, cardiac failure, hypertension, haematuria, and proteinuria, two weeks after an upper respiratory infection. He was admitted three weeks after these symptoms had appeared, when he was well on the way to recovery except for residual hypertension, proteinuria, and increased urinary excretion of red cells. He continued to improve, and eight months later no longer had protein in his urine. The main abnormality in the renal biopsy specimen was a proliferative change in some glomerular tufts.

Summary

1. Renal biopsies were performed in 14 cases of acute glomerular nephritis within 17 days of the onset of symptoms, and in one case after six weeks.

2. In three cases there were only minor changes in the epithelium of Bowman's capsule. Clinically these patients had oedema and cardiac failure without proteinuria, haematuria, or hypertension.

3. Eleven patients showed extensive abnormalities in the glomerular tufts. These lesions consisted of varying degrees of nuclear proliferation, polymorph infiltration, and an increase of eosinophilic internuclear material. Six of these patients also had focal areas of severe tubular degeneration and inflammatory cell infiltration of the interstitial tissue.

4. Microscopic lesions of the glomerular tufts were always associated with proteinuria, and usually with haematuria; the blood-pressure, blood-urea, and creatinine clearance were also related to these structural changes, though not with such consistency.

5. Two patients had severe impairment in the ability to concentrate the urine; both had multiple tubular lesions.

6. An erythrocyte sedimentation rate greater than 55 mm. in one hour was good evidence of widespread renal damage with interstitial and tubular lesions.

7. Only two patients had proteinuria for more than a year; in addition to glomerular changes, both had numerous tubular lesions.

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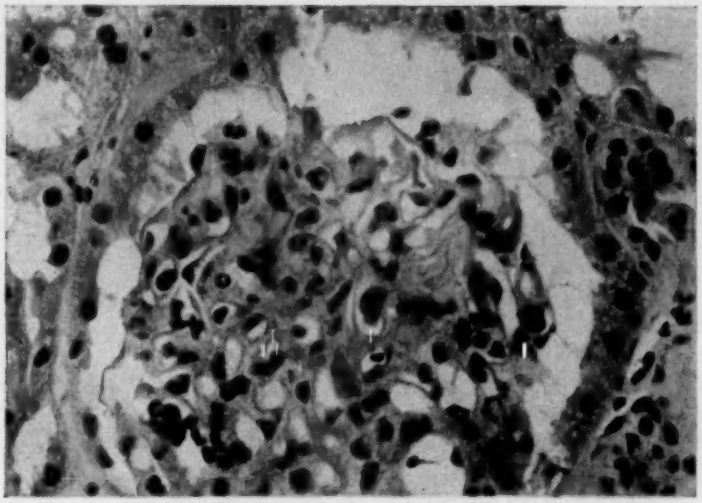

FIG. 7. Case 1. Glomerulus showing 'tubularization' of the epithelium of Bowman's capsule
(haematoxylin and eosin, × 500)

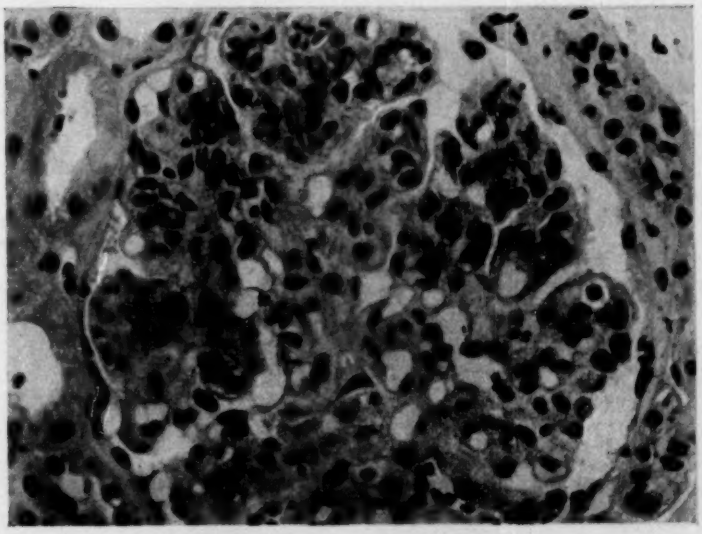

FIG. 8. Case 4. Glomerulus showing focal nuclear proliferation and polymorph infiltration
(haematoxylin and eosin, × 500)

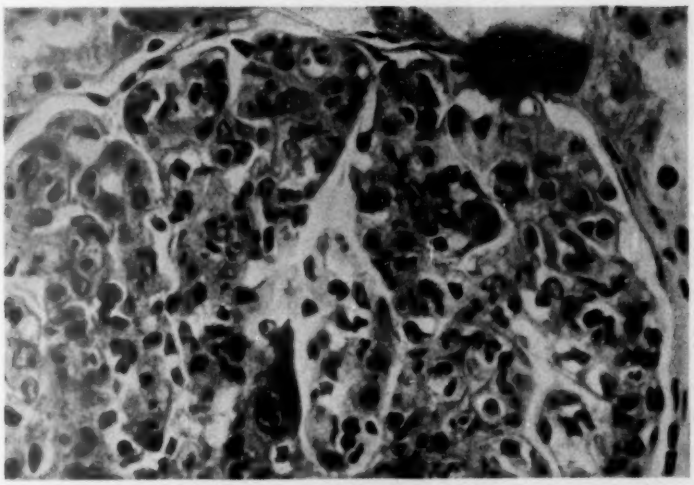

FIG. 9. Case 5. Glomerulus which is greatly enlarged, with widespread nuclear proliferation and polymorph infiltration (haematoxylin and eosin, ×500)

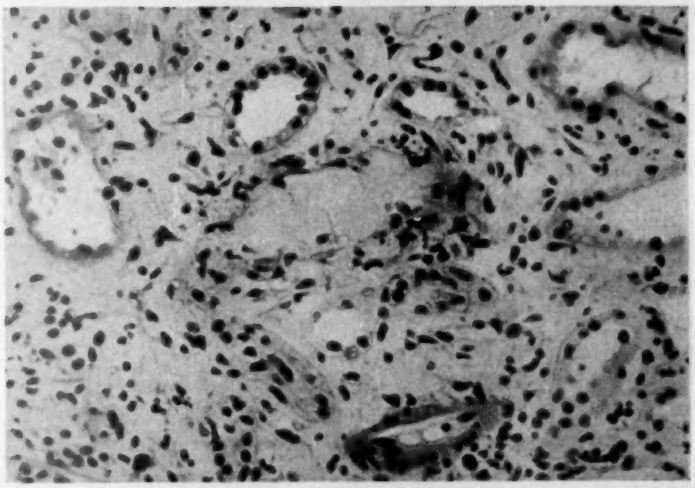

FIG. 10. Case 13. Tubular degeneration and necrosis, with oedema and inflammatory cell infiltration of interstitial tissue. A number of eosinophils are present in the inflammatory exudate (haematoxylin and eosin, ×280)

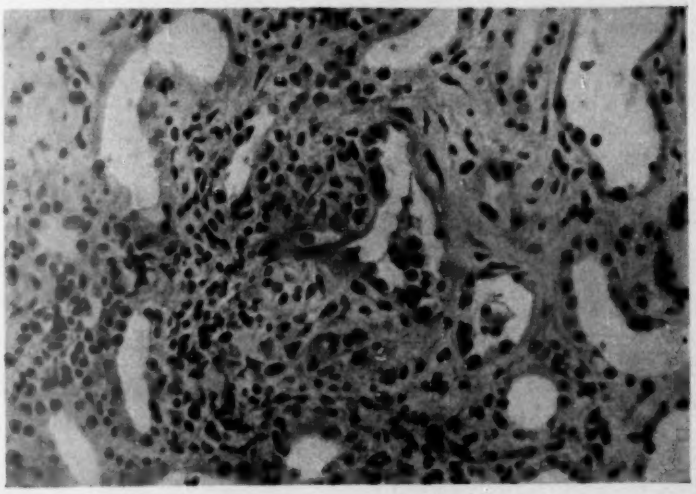

FIG. 11. Case 12. Degeneration and necrosis of tubular epithelium associated with oedema and inflammatory cell infiltration of interstitial tissue. The latter includes a few neutrophils and eosinophils (haematoxylin and eosin, ×280)

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HYPERTENSION AND DIABETES MELLITUS[1]

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During a systematic search for phaeochromocytoma in diabetic patients (Freedman, Moulton, Rosenheim, Spencer, and Willoughby, 1958) the blood-pressure was measured in a large number of subjects attending a diabetic clinic. In the course of this investigation the observers were impressed by the high incidence of hypertension in diabetic patients, which at first appeared to confirm the conclusions reached by Marañon (1922), Hitzenberger and Richter-Quittner (1921), Kylin (1923), Koopman (1924), Klein (1924), Bell and Clawson (1928), Bell (1946), and Balme and Cole (1951), and the opinions expressed by such authorities as Joslin (Joslin, Root, White, and Marble, 1952) and Fishberg (1954). Balme and Cole (1951) stated that 'it is certain that diabetics tend to show hypertension and atheroma more than non-diabetics', and supported this opinion with the results of their own observations in 209 diabetics, and those from seven previous studies. Härle (1921) even suggested that hypertension might be the cause of diabetes, while Marañon (1922), finding that the incidence of hypertension was greater at all ages in diabetics than in non-diabetics, concluded that hypertension was a pre-diabetic condition. Adams (1929), however, found no significant difference in the average blood-pressure of diabetics and normal subjects, and considered that diabetes did not predispose a patient to hypertension. Sherrill (1933), in an analysis of 425 diabetic patients, also found no evidence that diabetes was a specific factor in increasing the blood-pressure, and pointed out that hypertension and diabetes were both predominantly diseases of the sixth decade, and would therefore frequently occur together. He also noted the high incidence in elderly diabetics of obesity and peripheral vascular disease, which are known to be associated with hypertension. Major (1929), in a careful study of 408 diabetics, concluded that the systolic blood-pressure was only slightly raised, and that the diastolic pressure was not significantly higher than in a general hospital population, except in the age group 65 to 70 years. Pickering (1955), in a preliminary note on 500 diabetics, stated that the systolic blood-pressure was a little higher and the diastolic pressure a little lower than in a control series, but doubted whether the differences were significant.

Since there is still a divergence of opinion concerning the incidence of hypertension in diabetes, and as many of the previous studies were based on small numbers of patients, the results and methods of analysis employed in the

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present survey of 1,100 diabetics are given in detail. It was surprising to find that the statistical analysis did not support the clinical impression gained by the observers. Earlier reports were therefore scrutinized and, whenever possible, subjected to the same methods of analysis before comparison with the results obtained in the present investigation. Concepts of hypertension have changed greatly since many of the studies of high blood-pressure in diabetics were made, and it is no longer regarded as a disease *sui generis*, but as a manifestation of one or more factors operating on the cardiovascular system. This multifactorial approach has its most obvious application in the separation of aetiologically distinct varieties of hypertension, such as those associated with thyrotoxicosis, overactivity of the adrenal medulla or cortex, diabetic nephropathies, pyelonephritis, and haemochromatosis. The patients in the present study have been cla sified on this basis. The recently recognized importance of the arm-circumference in the measurement of blood-pressure (Ragan and Bordley, 1941; Pickering, Roberts, and Sowry, 1954; Fletcher, 1954) has also been applied for the first time to a series of diabetic patients.

Patients Investigated and Methods

The observations were made on 1,100 diabetic patients who attended the University College Hospital clinic during a period of 12 months from October 1955 to September 1956. Records were kept on special forms and subsequently analysed.

Statistical methods. Levels of probability were obtained by applying Fisher's '*t*' test (Fisher, 1946) to the standard errors of the difference between two proportions calculated by the method given by Hill (1955).

The blood-pressure was measured with the patients sitting at a table, after they had rested for 15 minutes. Mercury manometers with a cuff 13 cm. wide were used, and the diastolic pressure was recorded at the point when the sounds faded abruptly.

Arm-circumference and blood-pressure. Ragan and Bordley (1941) compared the direct measurement of the blood-pressure by arterial puncture and Hamilton manometer with that obtained simultaneously by the indirect auscultatory method. They found that the indirect reading was higher than the true arterial pressure in patients with large arms. Pickering, Roberts, and Sowry (1954) considered that it was useful, in comparing groups of patients, to make an allowance for arm-circumference, and we have therefore analysed our data both before and after applying their correction factor. The arm-circumference was measured in cm. at the mid-point of the upper arm, with the forearm extended.

Criteria of essential hypertension. In our view the term essential hypertension does not describe a particular disease. The group so referred to in the present paper includes all the diabetic patients with a diastolic blood-pressure of 100 mm.Hg or more after the arm-circumference allowance had been applied, in whom no specific aetiological factor could be identified. Subdivision, as for

example a separation of patients with senile arteriosclerotic hypertension, was not considered justifiable, for reasons which are given in the discussion.

Criteria of diabetic intercapillary glomerulosclerosis. Patients with hypertension were considered to have a diabetic nephropathy if they had a persistent proteinuria of two parts per 1,000, or more. Other causes of proteinuria, such as pyuria and haematuria, were excluded.

TABLE I

The Age and Sex Distribution of 1,100 Diabetic Patients attending the University College Hospital Clinic, and of a Control General Hospital Population

MALE PATIENTS

Age group (years)	Normal			Diabetic			S.E.D.	D	Level of significance P
	Total	Hypertensive Number	%	Total	Hypertensive Number	%			
0–9	0	0	..	9	0	0	..	..	..
10–19	46	0	0	34	0	0	..	..	..
20–29	142	1	0·7	55	0	0	0·8	0·7	0·4
30–39	180	2	1·1	70	1	1·4	1·4	0·3	0·8
40–49	178	9	5	74	5	6·8	3·4	1·8	0·6
50–59	147	21	14·3	105	17	16·2	4·6	1·9	0·7
60–69	98	23	23·4	65	20	31	7·1	7·6	0·1
70–79	31	9	29	16	13	81	12·6	52	0·001
80+	5	2	40	0	0	..	..	..	..
Total	827	67	8·1	428	56	13·1	..	..	..

FEMALE PATIENTS

Age group (years)	Normal			Diabetic			S.E.D.	D	Level of significance P
	Total	Hypertensive Number	%	Total	Hypertensive Number	%			
0–9	0	0	..	8	0	0	..	..	..
10–19	73	0	0	35	0	0	..	..	..
20–29	171	0	0	55	0	0	..	..	..
30–39	227	10	4·4	68	1	1·5	1·9	2·9	0·15
40–49	236	24	10·2	111	7	6·4	2·9	3·8	0·2
50–59	239	54	22·6	211	36	17·2	3·7	5·4	0·85
60–69	161	58	36	133	49	37	5·9	1	0·85
70–79	86	33	38·4	51	47	92	6·5	53·6	0·001
80+	11	4	36·3	0	0	..	..	..	..
Total	1,204	183	15·2	672	140	20·8	..	..	..

S.E.D. = Standard error of the difference between two proportions.
D = Difference between two proportions.

Criteria of pyelonephritis. The group here described contains all the diabetic patients with a diastolic blood-pressure of 100 mm. Hg or above who had recurrent or persistent symptoms of a urinary-tract infection, associated with an excess of pus-cells and with pathogenic bacteria in the urine.

Results

Overall incidence of hypertension in diabetes. The numbers of diabetic subjects in the present study, grouped according to age and sex, are given in Table I, and the frequency distributions in Fig. 1. Female (672) were more numerous

than male patients (428), especially between the ages of 50 and 79 years (395 women). The diastolic blood-pressure was 100 mm. Hg or more in 196 (17·8 per cent.) of 1,100 diabetic patients attending the University College Hospital clinic. The numbers of hypertensive diabetic patients, grouped according to diagnosis, age, and sex, are given in Table II. In both male and female diabetics the absolute number and proportional incidence of hypertension rises continuously with increasing age, until at 70 to 79 years 92 per cent. of the women

TABLE II

The Distribution according to Age, Sex, and Diagnosis of 196 Hypertensive Diabetic Subjects

	30–39 years		40–49 years		50–59 years		60–69 years		70–79 years		Total
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	
Essential hypertension	0	0	1 (1·3%)	0	7 (6·7%)	14 (6·6%)	9 (14%)	27 (20%)	6 (38%)	25 (49%)	89
Diabetic glomerulosclerosis	1 (1·4%)	1 (1·5%)	3 (4·2%)	2 (1·9%)	6 (5·7%)	6 (2·7%)	6 (9%)	8 (6%)	5 (31%)	16 (31%)	54
Fat arm only	0	0	1 (1·3%)	4 (3·6%)	4 (3·8%)	11 (5·2%)	3 (4·6%)	12 (9%)	2 (12%)	6 (12%)	43
Thyrotoxicosis	..	..	..	1	..	..	..	..	..	..	1
Cushing's disease	..	..	..	..	..	3	..	..	..	..	3
Haemochromatosis	..	..	..	..	..	1	..	..	..	..	1
After toxaemia of pregnancy	..	..	..	..	..	1	..	..	..	..	1
Heart block	..	..	..	..	..	..	1	..	..	..	1
Pyelonephritis	..	..	..	..	..	..	1	2	..	..	3
Total	1	1	5	7	17	36	20	49	13	47	196
Percentage of diabetics with hypertension in each age and sex group	1·4	1·5	6·8	6·4	16·2	17·2	31	37	81	92	

and 81 per cent. of the men have a diastolic pressure of 100 mm. Hg or more (Table I and Fig. 2). Among diabetic patients of all ages, the absolute number of female patients with hypertension is greater than the corresponding figure for male patients, and this difference is most evident between the ages of 50 and 79 years, where there are 132 women with hypertension and only 50 men. The proportion of patients with hypertension is also greater among diabetic women than among diabetic men in all age groups over 50 years (Table I).

Arm-circumference factor. The arm-circumference was measured (see above) in all patients with hypertension. When the arm-circumference factor was applied, the adjusted diastolic blood-pressure was below 100 mm. Hg in 43 of these subjects (21 per cent. of the hypertensive diabetics). The absolute number and the proportion of these patients in each age and sex group are given in Table II and Fig. 3. In an additional nine patients (4·6 per cent. of the hypertensive diabetics) this correction factor reduced the diastolic pressure by 10 mm. Hg or more, although the adjusted value was still over 100 mm. Hg. The absolute incidence of 'hypertension' due to an obese arm was greatest at 50 to 69 years, and at all ages it was much more common in female than in male patients. The proportional incidence of this apparent hypertension increased steadily with age (Fig. 3). In addition, there were 15 obese diabetic patients, not included in this series, whose original diastolic blood-pressure reading was over 100 mm. Hg. After treatment with a low-calorie diet they lost weight, and at the time of this survey the diastolic blood-pressure in all of

them was less than 100 mm. Hg. Of the 43 patients included in the 'obese arm' category, six (14 per cent.) gave a clear family history of hypertension or cardiovascular disease.

Essential hypertension. Table II and Fig. 3 give the absolute number and relative incidence of cases of essential hypertension in each age and sex group.

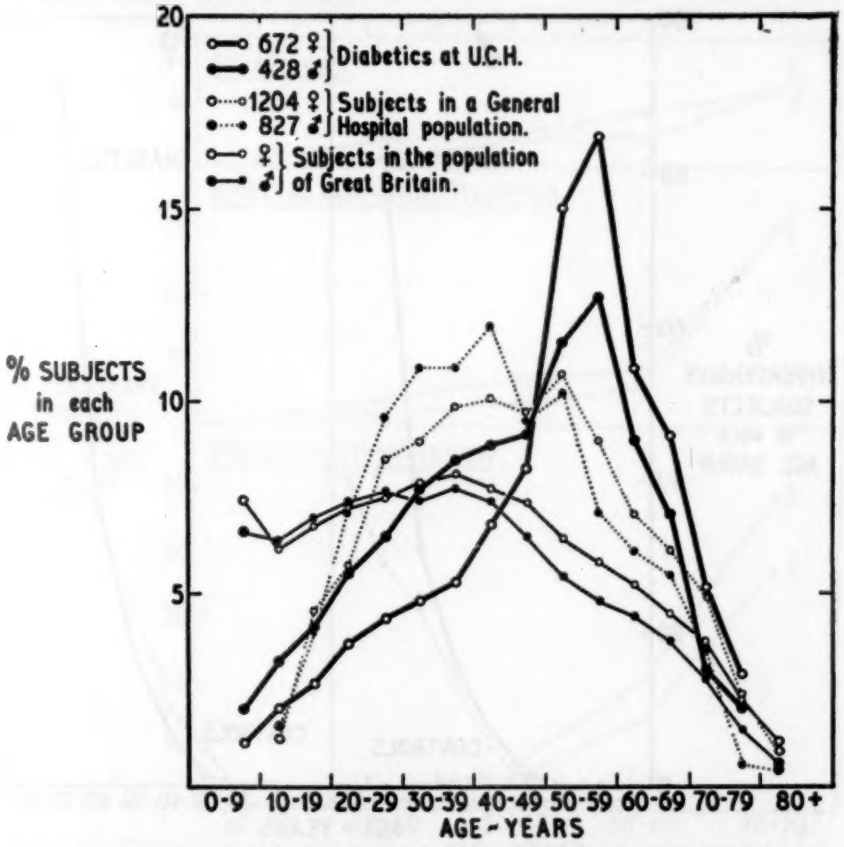

FIG. 1. The frequency distribution by age of the diabetic patients attending University College Hospital, of a general hospital population, and of the population of Great Britain (Report of the Royal Commission on Population, 1949).

The total number of such patients was 89 (8 per cent. of the total; 45 per cent. of the hypertensive diabetics). There were more women (66) than men (23), and at 60 to 69 years the relative incidence was 20 per cent. in the women compared with 14 per cent. in the men. From 40 to 79 years of age the absolute number and relative incidence of cases of essential hypertension increased with advancing age, until at 70 to 79 years 49 per cent. of the female and 38 per cent. of the male diabetics were included in this category. In 49 (55 per cent.) of the patients with essential hypertension the pulse-pressure was high and there was evidence of gross thickening of the peripheral arteries. These patients were all

over 60 years old, and would usually be considered to have arteriosclerotic or senile hypertension. Since many were known to have had hypertension for years before there was clinical evidence of peripheral vascular disease, the separation of arteriosclerotic senile hypertension was considered to be unjustified. An unequivocal family history of hypertension or cardiovascular

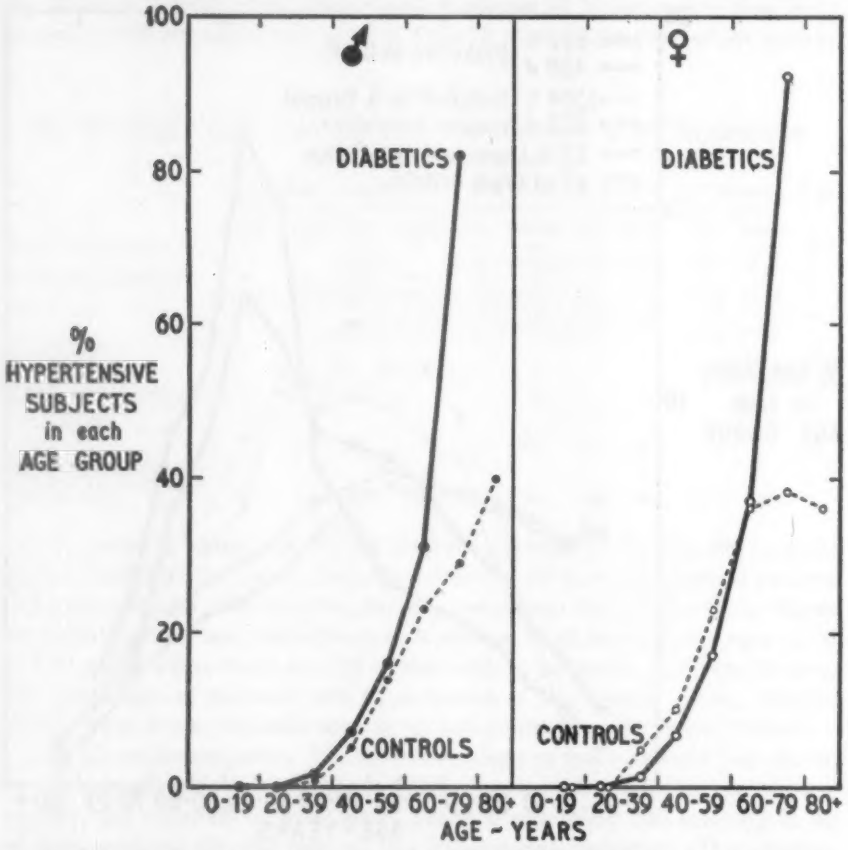

FIG. 2. The frequency distribution by age and sex of subjects with a diastolic blood-pressure of 100 mm. Hg or above in 1,100 diabetic patients (672 female and 428 male subjects) and 2,031 non-diabetic patients (1,204 female and 827 male subjects).

disease was obtained in 30 of the 89 patients with essential hypertension (33·7 per cent.).

Diabetic nephropathy. Table II and Fig. 3 give the absolute numbers of cases, and relative incidence, of diabetic nephropathy as a probable cause of hypertension in each age and sex group. There were 54 instances of this complication (4·9 per cent. of the total series; 27·5 per cent. of the hypertensive diabetics). The numbers and the proportion increased steadily with age, and at 70 to 79 years reached a maximum incidence of 31 per cent. in both sexes. More women

than men had hypertension associated with diabetic nephropathy, but, when corrected for the age distribution of the diabetic population, the sex incidence was not significantly different. The probable errors in the clinical diagnosis of diabetic nephropathy are considered in the discussion. Most (87 per cent.) of the patients with hypertension and diabetic glomerulosclerosis did not have a family history of hypertension.

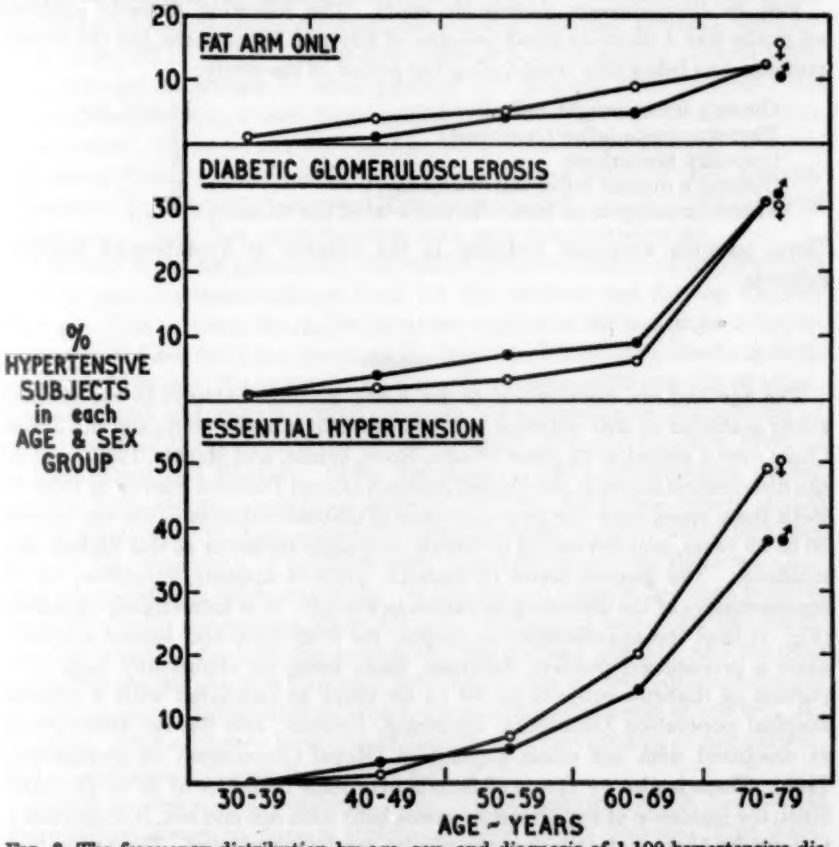

FIG. 3. The frequency distribution by age, sex, and diagnosis of 1,100 hypertensive diabetic patients.

Pyelonephritis. Eight hypertensive diabetic patients had evidence of infection in the urinary tract. Three of these patients were considered to have hypertension due to pyelonephritis; in the other five the infection was associated with some other aetiological factor, such as intercapillary glomerulosclerosis.

Thyrotoxicosis. There were 14 (1·2 per cent.) diabetic patients with clinical evidence of thyrotoxicosis confirmed by radioactive iodine studies. Ten (71 per cent.) of these originally had a diastolic blood-pressure of 100 mm. Hg or above. After treatment of the thyrotoxicosis the diastolic blood-pressure fell below this level in nine patients, and in one it was unchanged.

Other endocrine and metabolic disorders. Three patients with Cushing's disease, and one with haemochromatosis, were among the patients with hypertension and diabetes seen in the diabetic clinic during the period of study. In addition, two patients with diabetes and hypertension due to phaeochromocytoma, and one patient with diabetes associated with acromegaly, were seen and treated by the authors, but are not included in this series.

Fall in blood-pressure during the study. The following diabetic patients originally had a diastolic blood-pressure of 100 mm. Hg or more, but the blood-pressure was below this level during the period of the study:

Obesity (after weight reduction)	14 patients
Thyrotoxicosis (after treatment)	8 ,,
Coronary thrombosis	4 ,,
Cushing's disease (after adrenalectomy)	2 ,,
Phaeochromocytoma (after the removal of the tumour)	2 ,,

These patients were not included in the number of hypertensive diabetic subjects.

Discussion

The age and sex distribution of the living diabetic patients in the present study is similar to that recorded in 7,365 diabetic subjects attending the Joslin Clinic over a period of 25 years (Joslin, Root, White, and Marble, 1952), and to the distribution found in the United States National Diabetic Survey in 1935–6. Both these series show the preponderance of diabetic subjects in the age groups 50 to 69 years, and the excess of female over male diabetics at this highest age incidence. The present series of diabetic patients appears, therefore, to be representative of the diabetic population as a whole. It is immediately apparent (Fig. 1) that the age-distribution graphs, for both male and female subjects, show a pronounced positive skewness, there being an abnormally large proportion of diabetic subjects at 50 to 69 years as compared with a general hospital population (Hamilton, Pickering, Roberts, and Sowry, 1954*a*), and as compared with the whole population (Royal Commission on Population, 1949). There is also an excess of female over male diabetics at 50 to 79 years. Since the incidence of hypertension varies both with age and sex, it is necessary to consider these factors before the results can be interpreted. The proportion of hypertensive diabetics in each age and sex group has therefore been calculated, and the figures are compared with control data derived in the same manner from a general hospital population.

It is impossible to compare the incidence of hypertension in diabetic patients with that in the population as a whole, since this figure is unknown. Published data regarding the blood-pressure in large numbers of individuals have necessarily been obtained from selected groups, as for example in industrial workers (Master, Dublin, and Marks, 1950), insurance policy holders (Robinson and Brucer, 1939), and university students (Alvarez, 1923). The results naturally differ according to the method of sampling. No general hospital population is

likely to have precisely the same age and sex distribution as the general population. This is true of the present control series (Fig. 1). It follows that, when the incidence of hypertension is considered, allowance for anomalies in distribution should be made, either by a calculated age-and-sex adjusted score (Hamilton, Pickering, Roberts, and Sowry, 1954*b*), or by plotting the results as a percentage of male and female persons in each age group. The hospital population may differ not only numerically from the general population, but also quantitatively in regard to the level of the blood-pressure. For example, there is likely to be a larger proportion of obese patients and subjects with varicose veins in a hospital group, and both these conditions show a positive correlation with hypertension. These factors were considered by Hamilton, Pickering, Roberts, and Sowry (1954*a*), who concluded that the results obtained in their hospital population 'represent the behaviour of the casual arterial pressure in the general population'. Their data have therefore been used as a control series.

A further difficulty arises from the widely different criteria of hypertension used in previous investigations, both for the controls and for the diabetic patients. This particularly applies to earlier reports on the incidence of hypertension in diabetic subjects: for example, Balme and Cole (1951) used a systolic pressure of 160 mm. Hg or more, or a diastolic pressure of 95 mm. Hg or more; Kramer (1928) and Sherrill (1933) a systolic blood-pressure of 150 mm. Hg or more. Some of the published results are in whole (Bell and Clawson, 1928) or in part (Root and Sharkey, 1936; Martensson, 1950) retrospective studies starting from autopsy records of diabetic subjects. Such data clearly should not be compared with those obtained in living patients, as there would probably be a higher proportion of subjects with hypertension among those who had died compared with those surviving. In the present series it has been possible to make a valid comparison, since the same method of measuring the blood-pressure was used for both the control and the diabetic patients, and the data compared are the absolute numbers, and the frequency distribution according to age and sex, of living subjects with a diastolic blood-pressure of 100 mm. Hg or above. This arbitrary level was chosen for the convenience of comparison, and no special significance is attached to it.

Overall incidence of hypertension. The present survey clearly shows that hypertension is very common in middle-aged and elderly diabetics (Figs. 2 and 3; Tables I and II), and that the incidence steadily increases with age, to reach a maximum of 81 per cent. in the male and 92 per cent. in the female subjects at ages over 69 years. When no allowance is made for anomalies of age and sex distribution of the diabetic population, the overall incidence of hypertension is greater in diabetes both in male subjects (13·1 per cent. in diabetics, 8·1 per cent. in non-diabetics) and in female subjects (20·8 per cent. in diabetics, 15·2 per cent. in non-diabetics). If the incidence is expressed as a proportion of each age and sex group, then from 10 to 69 years in both sexes there is no significant difference in the incidence of hypertension in diabetic and non-diabetic subjects. From 70 to 79 years high blood-pressure is much more common in diabetic men (diabetics 81 per cent., non-diabetics 29 per cent.)

and women (diabetics 92 per cent., non-diabetics 38·4 per cent.), and both these differences are significant at a level of probability of $P = 0{\cdot}001$. The excess of hypertensive subjects in the elderly diabetics is associated with a high incidence of gross arteriosclerosis (56 per cent. in women and 44 per cent. in men) and obesity (12 per cent. in men and women) in this age group, and with the added presence of hypertension due to diabetic nephropathies (31 per cent. in men and women). In the hypertensive diabetic subjects the number of female patients (140; 20·8 per cent.) greatly exceeds that of male patients (56; 13·1 per cent.); but the proportional incidence of high blood-pressure is only slightly greater in diabetic women than in diabetic men from 50 years onwards ($P = 0{\cdot}05$).

The present study shows that the clinical impression of an abnormally high incidence of hypertension in diabetics is largely due to the excessive numbers of diabetic subjects in the age groups in which high blood-pressure most commonly occurs. Earlier reports stating that hypertension is more common in diabetics have therefore been re-examined. In the series of Hitzenberger and Richter-Quittner (1921) there were 38 hypertensive patients, but only seven of these were diabetics. Marañon (1921) reported that 58 per cent. of diabetics over 50 years old had a systolic pressure of 180 mm. Hg or above, which compares with 19·9 per cent. for both sexes in Hamilton, Pickering, Roberts, and Sowry's (1954*a*) series of general hospital patients in the same age groups at that level of systolic blood-pressure. This appears to be a clear difference, but there were only 43 patients over 50 years in Marañon's series, and, if the data had been divided into five-year or 10-year age groups, the numbers in each group would have been too small for any difference to reach a level of significance greater than $P = 0{\cdot}1$. The same objection applies to the surveys of Klein (1924) on 120 diabetics, and Koopman (1924) on 161 diabetics. Balme and Cole (1951) reported on 209 diabetic patients, and stated that 'diabetics over 30 years old show a considerably higher incidence of hypertension than that found in the general population'. Again, when this series was divided into five-year age and sex groups, and a statistical comparison made with the control series of Wetherby (1932) or Hamilton, Pickering, Roberts, and Sowry (1954*a*), any differences in the incidence of hypertension were found to have significance at a level of probability of only $P > 0{\cdot}05$, except at ages over 60 years. Balme and Cole found that the incidence of hypertension in diabetics rose to 64 per cent. in men and 83 per cent. in women at 70 years and above, and these percentages were significantly higher than in the control series ($P = 0{\cdot}001$). Their results are, therefore, similar to those found in the present study. The report of Sherrill (1933) on 425 diabetics, and the careful statistical analysis made by Major (1929) on 408 diabetics, are in agreement with the results obtained in our survey. Major (1929) found that the proportion of subjects with a diastolic blood-pressure of 100 mm. Hg or more was not significantly higher in the diabetic patients than in a general hospital population except at 65 to 70 years.

Arm-circumference factor. Since an allowance for the arm-circumference has not been applied to previous studies of hypertension in diabetes, we have not

used one in the calculation of the overall incidence of high blood-pressure. In the present study the arm-circumference factor was sufficiently large to reduce the diastolic blood-pressure below 100 mm. Hg in 21·9 per cent. of the patients with apparent hypertension. In a further 4·6 per cent. this correction reduced the diastolic pressure by at least 10 mm. Hg, although the adjusted value remained over 100 mm. Hg. The arm-circumference was important, therefore, in determining the blood-pressure as obtained by the auscultatory method in 26·5 per cent. of the hypertensive diabetic patients. The significance of obesity in relation to the level of the blood-pressure is further illustrated by the 15 diabetic patients who originally had a diastolic pressure of 100 mm. Hg or more, which fell below this value after reduction in weight. Fletcher (1954) observed, in a series of obese women, that after loss in weight there was a fall both in the observed blood-pressure and in the pressure corrected for the change in arm-circumference consequent on weight reduction.

Hypertension due to diabetic nephropathy. Although there was a maximum incidence of intercapillary glomerulosclerosis in 31 per cent. of both sexes, the overall incidence of this complication was only 4·9 per cent., or 27·5 per cent. of the hypertensive diabetics. This figure is less than that reported by other workers. Wilson, Root, and Marble (1951) found an incidence of 25 per cent., but this was in a selected group of patients with long-standing diabetes, whereas the present series included many patients who had had diabetes for a few years only. Lambie and MacFarlane (1955) reported an incidence of 55 per cent.; but this percentage was based on a histological diagnosis in a post-mortem series, and only 10 (8·2 per cent.) of these patients had the clinical syndrome as judged by the criteria used in the present study. Oedema was present in 62 per cent. of our patients in this group, and in 58 per cent. the serum-albumin was less than 3·5 g. per 100 ml. Most of our patients also had diabetic retinopathy (97 per cent.) and peripheral neuritis (84 per cent.). It will be apparent that many of our patients in this group had advanced diabetic nephropathy. Renal biopsy studies (Joske, 1956) appear to show that intercapillary glomerulosclerosis may exist in the absence of the clinical syndrome. It is highly probable, therefore, that the incidence of this complication has been underestimated in our series. In spite of this circumstance, diabetic nephropathy was a numerically important cause of hypertension, accounting for 27 per cent. of all the cases in which the diastolic blood-pressure was over 100 mm. Hg.

Pyelonephritis. It is noteworthy that most of our diabetic patients with recurrent urinary infections did not have hypertension, and that this complication accounted for only three (1·5 per cent.) of the hypertensive diabetic subjects. It is probable that some patients who had pyelonephritis without symptoms, or who did not have pyuria at the time of examination, may have been included in the category of essential hypertension.

Essential hypertension. Apparent essential hypertension was common in diabetics, and rose to a maximum incidence of 49 per cent. of the women and 38 per cent. of the men at 70 to 79 years (Table II; Fig. 3). As there are no figures available for the incidence of essential hypertension in a general popula-

tion, no comparison can be made. An unequivocal family history of hypertension or cardiovascular disease was obtained from 33·7 per cent. of the diabetic patients who were considered to have essential hypertension. This compares with 37 per cent. in a similar but smaller series of hypertensive diabetics (Balme and Cole, 1951). The manifold difficulties in obtaining and interpreting a family history of hypertension or cardiovascular disease have been discussed by Platt (1947) and Hamilton, Pickering, Roberts, and Sowry (1954*c*). It is considered that definite conclusions concerning the familial incidence of hypertension can be made only when the blood-pressure has actually been measured in all the first-degree relatives, and the measurement subsequently adjusted for age and sex (Hamilton, Pickering, Roberts, and Sowry, 1954*b*).

Severity of hypertension in diabetics. Even when all aetiological types of hypertension other than phaeochromocytoma were considered, severe hypertension was uncommon in the diabetic patients. The incidence of an uncorrected diastolic blood-pressure of 125 mm. Hg or above in the diabetic subjects was 0·5 per cent. for the male and 1·4 per cent. for the female patients. This compares with an incidence of 0·7 per cent. for male and 2·1 per cent. for female subjects in a general hospital population (Hamilton, Pickering, Roberts, and Sowry, 1954*a*). None of the patients attending the University College Hospital diabetic clinic had malignant hypertension, nor was clear evidence of grade III hypertensive retinopathy found in any patient. Of the four cases of phaeochromocytoma recently reported with abnormalities of carbohydrate metabolism, one patient had grade IV retinopathy and one had grade III changes (Freedman, Moulton, Rosenheim, and Spencer, 1958).

Summary and Conclusions

1. The blood-pressure was measured in 1,100 patients attending a diabetic clinic, and the data have been analysed in terms of the incidence of hypertension in each age and sex group.

2. Hypertension was common in both sexes, and the incidence steadily increased with age to a maximum of 92 per cent. of the female and 81 per cent. of the male diabetics at 70 to 79 years.

3. A strong clinical impression was gained that hypertension was more common in diabetics than in a general hospital population. Statistical analysis, however, clearly shows that this difference is largely a false impression due to the abnormal age and sex distribution of the diabetic population. From 10 to 69 years of age, in both sexes, there was no significant difference in the incidence of hypertension in diabetics as compared with a non-diabetic population ($P > 0{\cdot}05$). It was only at 70 to 79 years that high blood-pressure was distinctly more common in diabetics ($P < 0{\cdot}001$).

4. Severe hypertension (diastolic pressure over 125 mm. Hg) is rare in diabetes, the incidence being 0·5 per cent. in the male and 1·4 per cent. in the female subjects, which is less than in a general hospital population. Advanced

hypertensive retinopathy (grades III and IV), excluding diabetic retinopathies, was not seen in any of the diabetic subjects, except those with phaeochromocytoma.

5. Data are given of the apparent incidence of hypertension due to various renal and endocrine disorders in diabetes. Diabetic nephropathies were diagnosed in 27·5 per cent. of the patients whose diastolic blood-pressure was over 100 mm. Hg.

6. The arm-circumference was measured in all the hypertensive diabetic subjects, and was found to be an important factor in determining the level of the blood-pressure in 26·5 per cent. of these patients.

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